Adopted: 12/5/16

Gastroesophageal reflux disease (GERD): Assessment & Management

Introduction

GERD occurs when refluxed gastric acid and pepsin cause bothersome symptoms and/or necrosis and inflammation of the esophageal mucosa. Some degree of reflux is normal and intermittent heartburn is also generally benign. Classic symptoms of GERD include recurrent episodes of retrosternal burning and regurgitation. The most common mechanism thought to cause reflux is excessive transient lower esophageal sphincter (LES) relaxation, which occurs in 90% of cases. Disruption of esophageal peristalsis, delayed gastric emptying, gastric hypersecretory states and hiatal hernias are other potential underlying pathologies that may also contribute to GERD development.

GERD is estimated to affect 13%–29% of the U.S. population.(Dent 2005; Straumann 2005) A typical full-time, allopathic family physician can expect to diagnose and treat 40 to 60 patients with this condition each month. (El-Serag 2004)

GERD Risk Factors

A variety of risk factors and mechanisms may lead to reflux disease. Risk factors include obesity (especially abdominal obesity), pregnancy, and smoking. (Kahrilas 2013) Ingestion of certain foods and medications, gastric distention from excessive eating, and lying recumbent or leaning forward after a meal are common triggers. See table below for a list of foods and medications known to cause symptoms. (Chan 2016)

FOODS THAT *MAY* TRIGGER GERD	MEDICATIONS THAT CAN CAUSE GERD (VIA DECREASED LES PRESSURE)
Caffeine	β-Adrenergic agonists, including inhalers
Chocolate	α-Adrenergic antagonists
Peppermint	Anticholinergics
Alcohol (red wine pH = 3.25)	Calcium channel blockers
Carbonated beverages (cola pH = 2.75)	Diazepam
Citrus fruits (orange juice pH = 3.25)	Estrogens
Tomato-based products (tomato juice pH = 3.25)	Narcotics
Vinegar (pH = 3.00)	Progesterone
Fatty foods	Theophylline

Overall Strategy

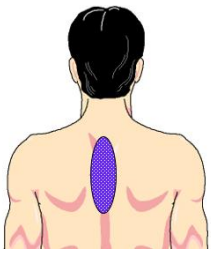
When caring for a patient with symptoms that suggest GERD, a number of clinical decisions must be made. This CSPE protocol provides a framework for this decision making process based on considering a series of clinical issues.

Clinical Issues

1: Does the presentation suggest GERD?
2: Are there any red flags?
3: Have competing diagnoses been considered?
4: Should the patient be referred for endoscopy?
5: What are the management options?
6. What are the prognostic and maintenance issues?

1: Does the presentation suggest GERD?

Heartburn and regurgitation are the typical symptoms of GERD. Heartburn, or pyrosis, is a burning sensation or sense of discomfort in the retrosternal chest (although the pain is sometimes felt in a broader area). Chest pain due to GERD usually does not radiate to the back. When radiation does occur, it is frequently located over the thoracic spine.



Regurgitation, or reflux, is the effortless return of swallowed solids or liquids into the oropharynx. Characteristically, patients will report an acidic or sour quality to the partially digested food. Some sources may refer to acid regurgitation of just liquids as water brash. Up to 70% of patients with GERD will be correctly identified by the characteristic symptoms of heartburn and regurgitation. (Aanen, 2006)

An initial diagnosis of GERD can be made clinically (without any testing) based on the presence of heartburn and/or regurgitation as long as there are no alarm symptoms (see pages 3-4).

Consideration may be given to the use of a validated diagnostic tool such as the GerdQ questionnaire to aid in diagnostic accuracy. The GerdQ was developed for use in primary care patients who report upper abdominal symptoms. It involves asking six questions about gastrointestinal (GI) symptoms and calculating a diagnostic score based on the frequency in which they occur. A score of 8 or above will correctly identify 80% of patients with GERD. GERD can also safely be ruled out in patients with a score of 0-2. (Jonasson 2013) See Appendix A.

Atypical GERD symptoms

Atypical Symptoms

- Chest pain
- Chronic cough
- Dysphagia
- Chronic sore/burning throat
- Hoarseness
- Globus sensation
- Belching

Dysphagia, belching, and epigastric or chest pain are atypical GI symptoms that may be an indication of GERD. Atypical presentations offer more of a diagnostic challenge. For example, ruling out a cardiac cause is essential in any patient who presents with chest pain.

GERD has also been implicated in causing the following extra-intestinal symptoms: chronic sore or burning throat, hoarseness, globus sensation (perception of a lump in the throat), wheezing, and chronic non-productive cough. A diagnosis of GERD should be considered if these non-GI symptoms are present. For example, GERD has been found to be present in up to 40% of nonsmoking patients with chronic cough in prospective cohort studies. (Mello 1996; Palombini 1999) It is among the top 3 most common causes of cough lasting at least 3 weeks in nonsmoking patients.

Although it is fairly common for patients with GERD to experience atypical symptoms, in the presence of atypical symptoms an empiric diagnosis of GERD can no longer be made. Options for diagnosis in these cases include a trial of acid suppression therapy, esophageal pH-monitoring and/or esophagogastroduodenoscopy (EGD).

Acid suppression with a proton pump inhibitor (PPI) medication is typically used to treat GERD but can also be used to establish the diagnosis in patients with non-cardiac chest pain. A 2005 meta-analysis of 6 studies found 80% sensitivity (95% CI, 71%-87%) and 74% specificity* (95% CI, 64%-83%) for a PPI acid suppression test for the diagnosis of GERD in patients with noncardiac chest pain.(Wang 2005) One small study demonstrated that relief of chest pain after a 14-day course of the PPI omeprazole 40 mg/d was more sensitive than endoscopy, manometry, or 24-hour esophageal pH monitoring in diagnosing GERD in patients with non-cardiac chest pain.(Pandak 2002)

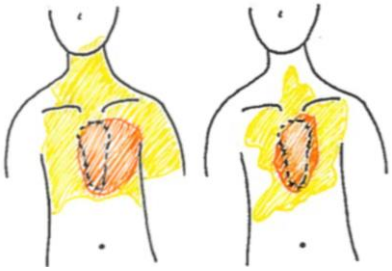
A therapeutic trial of high-dose PPI (i.e., omeprazole 40 mg twice daily) is appropriate as a test to confirm suspected GERD as the cause of non-cardiac chest pain as long as there are no red flags and the patient does not have a history of upper GI tract, esophagus, or thorax surgery.

* +LR = 3.0; -LR 0.3

2: Are there red flags?

Red flags (also called alarm symptoms) in a suspected GERD patient suggest the possibility of either serious complications of GERD or potentially life-threatening competing diagnoses. Difficulty swallowing (dysphagia) and chest pain are two of the important atypical GERD symptoms that are considered red flags. When a patient has chronic heartburn, regurgitation, and dysphagia, it may be an indication that the refluxed acidic stomach contents have led to erosion, stricture formation, precancerous lesions and/or cancerous growths in the esophagus. Chest pain, even when associated with regurgitation, must be considered as an alert to a possible cardiac cause for symptoms. Acute coronary syndrome (ACS) is one of the most dangerous and important competing diagnoses to consider as ACS is prevalent and symptoms can significantly overlap with GERD.

Warning: Chest pain locations overlap. Rule out cardiac chest pain early!



CARDIAC ANGINA **GERD**

Some symptoms that are usually associated with esophageal causes are not pathognomic and may also be occasionally present in atypical cardiac disease such as pain with swallowing, symptoms provoked by recumbency, relief with antacids, presence of regurgitation, and pain that awakens one at night. Likewise, patients who are appropriately referred for cardiac stress testing may actually have GERD. ***(See table below).***

SYMPTOM	CARDIAC PATIENTS	ESOPHAGEAL PATIENTS
Achy pain for hours	25%	78%
Awaken by pain	25%	61%
Provoked by swallowing	6%	39%
Provoked by recumbency or stooping	19%	61%
Pain comes on after exercise completed	4%	33%
Relieved by antacid	10%	44%
Heartburn	17%	78%
Regurgitation	17%	67%
GI symptoms	46%	83%

Additional red flags to be aware of include odynophagia[1], unintentional weight loss, early satiety, prolonged nausea and vomiting, GI bleeding, iron deficiency anemia, and ongoing symptoms despite appropriate medical treatment. Adequate medical therapy is generally considered to be an 8-week trial of over-the-counter proton-pump inhibitor medication. (Katz 2013) All **patients with alarm symptoms require endoscopic evaluation.**

Clinical warning: In patients over 50-60, maintain a high level of suspicion for serious diseases or complications because even serious pathology may present as mild GERD.

3: Consider competing diagnosis

Before settling on GERD as a provisional diagnosis, a number of competing diagnoses must be considered. The differential diagnosis for GERD could include coronary artery disease (CAD), peptic ulcer disease, functional dyspepsia, biliary colic, esophageal or gastric strictures, and eosinophilic esophagitis (EoE).[2] Complications of untreated GERD include erosive esophagitis and bleeding, strictures, Barrett's esophagus, and esophageal cancer. If CAD is a competing diagnosis for an individual patient, exclusion of a cardiac cause for symptoms is typically the first priority over investigating the GI etiologies (ACG strong recommendation, low level of evidence).(Katz, 2013)

It is important to try and differentiate between GERD and other etiologies based on patient presentation because evaluation and management differs. For instance, testing for *H. pylori* is often needed in patients with dyspepsia symptoms - epigastric pain or discomfort, bloating, early satiety, meal-associated fullness, nausea. Some studies recommend that *H. pylori* testing and treatment be done as the first step in evaluating dyspepsia, before any empiric treatment is initiated or endoscopy is performed. (Jarbol 2006; Duggan 2009) There may be situations, however, where a provider might choose to delay the *H. pylori* testing such as in the case of a young patient presenting with the symptoms of dyspepsia but also with a history of chronic NSAID use. In such a case, an empiric trial of PPIs and /or stopping NSAIDs for 2-4 weeks may be reasonable. Treatment failure would then trigger the *H. pylori* testing. Note that *H. pylori* testing is not a routine part of establishing the diagnosis of GERD.

[1] *Odynophagia* is painful swallowing and is distinguished from *dysphagia* (difficulty swallowing) and *globus* (sensation of a lump in the throat).

[2] EoE results in chronic, severe, immune/antigen-mediated inflammation of the esophagus and can cause dysphagia and food impaction in adults.

Step 4: Should the patient be referred for endoscopy?

Endoscopy can serve three different roles: 1) Rule in GERD in atypical presentations, 2) assess the degree of erosion, inflammation and esophageal complications (e.g., Barrett's esophagus – a potential precursor to esophageal cancer), and 3) diagnose other causes of the symptoms (e.g., ulcer or gastric cancer).

Most patients with typical GERD symptoms do not require initial endoscopy. It should be limited to patients who have red flags, including ongoing symptoms despite an adequate course (usually defined as 4-8 weeks) of PPI therapy (strong recommendation, moderate level of evidence).(Katz 2013) Alarm symptoms require endoscopic evaluation because they are often an indication that more serious pathology is occurring. One exception to this recommendation is that endoscopic screening for Barrett's esophagus may be warranted in men 50 years and older who have had GERD symptoms for at least 5 years without any red flags (evidence rating C)*. (Shaheen 2012)

Which patients with GERD should be screened for Barrett's esophagus?

Patients at high risk for GERD complications should be considered for Barrett's esophagus screening with endoscopy. This includes male sex, men and women over age 50, symptoms for >5 years, and obesity. (Katz 2012) Smoking may also play a significant role – see chart below. Studies have shown that regarding cost, it is most effective to screen white men over age 50 who have had symptoms for over 5 years. (Inadomi 2003; Shaheen 2012)

Risk factors for Barrett's esophagus among persons with GERD symptoms

Risk Factor	Odds Ratio
Smoking and self-reported weekly acid reflux*	51.4
BMI > 30 kg per m^2 and self-reported weekly acid reflux*	34.4
Self-reported weekly acid reflux*	29.7
GERD for more than 10 years ł	6.4
GERD for 5 to 10 years ł	5.0
Age > 40 years ǂ	4.9
BMI > 30 kg per m^2 ǂ	4.0
Hiatal hernia €	3.9
Male sex ¶	3.7
GERD for 1 to 5 years ł	3.0
Smoking (former or current)*	2.4
GERD < 1 year ł	1.0
Asian (compared with Caucasian) ¶	0.7
Hispanic (compared with Caucasian) ¶	0.5

* - Case-control study with 428 participants identified through two Australian pathology laboratories in a metropolitan area.
ł – Prospective observational study with 662 participants at U.S. community-based gastroenterology practice.
ǂ - Case-control study with 211 participants at a U.S. Veterans Medical Center.
€ - Multicenter, case-control study with 600 participants at eight Italian gastroenterology departments.
¶ - Prospective observational study with 517 participants at a U.S. Veterans Medical Center.

* A= Consistent, good-quality patient-oriented evidence
B= Inconsistent or limited-quality patient-oriented evidence
C= Consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Up to 10% of patients with chronic reflux symptoms will have Barrett's esophagus. (Taylor 2010) Although Barrett's esophagus can advance to esophageal adenocarcinoma, the *annual* risk of progression is low (approximately 0.12% to 0.33% per year).(Simmerman 2014)

5: What are the management options?

Management approaches can loosely be divided into non-pharmaceutical, pharmaceutical, and surgical. Empiric treatment can be initiated in the absence of alarm symptoms.

NON-PHARMACEUTICAL MANAGEMENT

Summary of non-pharmaceutical interventions

- Behavior changes (eating, sleeping, other lifestyle medications)
- Weight loss
- Dietary management
- Supplements (deglycyrrhizinated licorice, myrtle extract, aloe vera syrup, combined dietary supplementation of melatonin, vitamins and amino acids)
- Additional potential interventions (acupuncture, diagrammatic breathing training)

This management approach consists of 1) behavioral changes regarding eating, sleeping and other lifestyle modifications (e.g., clothing), 2) weight loss, 3) dietary management, 4) supplements, and 5) additional potential interventions. It is generally recommended to discuss these non-pharmaceutical treatment measures with each GERD patient as an individual may benefit from making suggested changes despite a lack of high quality, evidence-based data supporting some of this advice.

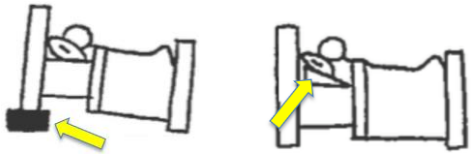
1) Behavioral/Lifestyle modifications

MEALS

- Eat smaller, more frequent meals. Avoid consuming large meals.
- Eating quickly may increase number of episodes (based on a small randomized crossover trial) but may be associated with a decrease of nocturnal reflux episodes (level 2 and 3 evidence). (Wildi, 2004)
- Avoid eating food 2-3 hours before lying down or going to sleep if GERD symptoms occur primarily at night (ACG conditional recommendation, low quality evidence, observational studies).(Katz, 2013) However, avoiding eating a meal 6 hours before going to bed did not change symptoms based on a small randomized cross over study.(Piesman, 2007)

SLEEPING BEHAVIORS

- Sleep in left decubitus position (improved pH but insufficient evidence on improving symptoms).
- Elevate head of bed to 30 degrees if GERD symptoms occur at night (ACG conditional recommendation, low quality evidence, observational studies; considered more effective than eliminating acidic or spicy foods).(Katz, 2013)
- Place 6 inch blocks under bed legs or a 4-6 inch Styrofoam wedge under mattress. Using pillows rather than foam wedges has not been shown to be as effective. (Pollmann 1996)



BLOCK **WEDGE**

- A small (N=15) cross over RCT demonstrated that elevating the head of the bed with a 10 inch wedge decreased the length of time of esophageal acid exposure compared to no wedge (from 21% to 15%). (Hamilton 1988)

CLOTHING

- Avoid abdominal compression (tight clothing, belts, etc.). This recommendation is based on evidence that patients who wear tight waist belts experience increased acid reflux but it has not been shown that avoiding tight clothing will necessarily alleviate symptoms. (Lee, 2015)

TOBACCO

- Stop smoking tobacco (CAG 2005). This should be recommended on general health principles, but may be especially helpful for smokers with GERD who are not overweight or obese (Ness-Jensen 2016). A large prospective cohort study (N=29,610) demonstrated that those who smoked had a significantly increased risk for severe reflux symptoms with an adjusted OR of 5.67 (95% CI 1.36-23.64) compared to those who stopped smoking. (Ness-Jensen 2014) The difference disappeared in patients that were overweight (BMI 25.0-29.9) or obese (BMI $\geq$ 30). Likewise, smoking cessation did not appear to improve symptoms in other observational studies in obese patients. (Katz, 2013)

2) **Weight loss**

Obesity is an important contributing factor to the development of GERD, and multiple studies have demonstrated that weight loss can reduce or even eliminate GERD symptoms (ACG conditional recommendation, moderate quality evidence; AGA grade B, observational studies). (Katz, 2013) This is true both if the patient is overweight/obese (BMI>25%) or if there has been recent weight gain in a normal weight person. In a 2006 study of women with weight in the normal range, patients with a

BMI increase of >3.5 units were nearly three times more likely to develop GERD and associated symptoms (OR = 2.8, 95% CI 1.63–4.84). (Jacobson 2006)

In one study of 332 adults with BMIs in the 25-39.9% range, weight loss over a period of 6 months resulted in 81% of patients experiencing a decrease in symptoms and 65% of patients with complete resolution of GERD. The average weight loss was 28.5 lbs. and the greater the weight loss, the more symptoms improved. (Singh M 2013) Weight loss paired with anti-reflux medications, such as PPIs, successfully decreased GERD symptoms even further in a large prospective population-based study. (Ness-Jensen 2013)

3) Dietary management

Traditionally, it has been usual practice to instruct patients to avoid foods that are viewed as common GERD triggers. Such foods include the following:

- Spicy foods
- Acidic foods (orange juice, tomatoes, etc.)
- Fatty foods
- Alcohol
- Caffeine
- Chocolate
- Mint
- Carbonated beverages

These recommendations were based on the fact that certain foods are known to affect lower esophageal sphincter (LES) function in ways that lead to more gastroesophageal reflux. For instance, fatty foods, alcohol, and chocolate are thought to decrease LES pressure and thus it was assumed that avoiding these foods would lead to improved pressure. Unfortunately, research has failed to demonstrate an increase in LES pressure with cessation of these substances. (Kaltenbach 2006) Therapeutic research has also failed to show clinically significant improvement in GERD symptoms with avoidance of the foods listed above.(Katz 2013) A systematic review of observational studies reported that there was no evidence linking carbonated beverages with GERD. (Johnson 2010)

Note: Current consensus guidelines therefore suggest that dietary limitations should not be made globally or routinely but rather should be individually targeted to a given patient that notes symptom changes when eating or eliminating a specific food. (Katz 2013; DeVault 2005)

Although the evidence is extremely limited, increasing dietary fiber may be a reasonable recommendation (Ness-Jensen 2016). One small RCT (N=15) reported that using a dietary fiber product for 2 weeks resulted in an increased number of days without heart burn (mean change 1.14 days) compared to placebo and reduced severity score by 4.6 points. (DiSilvesto 2011)

A very-low carbohydrate diet may be promising but the evidence is only preliminary and has not been subject to controlled or prospective trials. (Ness-Jensen 2016). A small (N=8) 6-day study of obese patients with GERD demonstrated a significant decrease in symptoms and duration of time that the esophagus was exposed to a pH <4 when consuming less than 20g/day. (Austin 2006) A brief series of 5 case reports reported rapid improvement in GERD symptoms in obese patients participating in a very-low carbohydrate diet. (Yancy, 2001)

4) Supplements

DEGLYCYRRHIZINATED LICORICE (DGL)

Deglycyrrhizinated Licorice (DGL) is recommended for consideration as a nutritional supplement to alleviate GERD symptoms. It is chosen as a potential GI therapy because of its antiulcer, antiinflammatory and antispasmodic effects. (Bone, 2013) Currently there are no studies specifically addressing DGL use in GERD patients, but DGL and other licorice extracts have been shown effective for peptic ulcer and aphthous ulcer in related controlled research. (Morgan 1982, Morgan 1985, D'imperio 1978, Moghadamnia 2009, Burgess 2008) There is also some evidence that pyrogastrone, a medication containing a derivative of glycyrrhizin (carbenoxolone) in combination with antacid and alginate, may be useful for esophageal healing. A double blind trial (Reed, 1978) and a double blind RCT (Young, 1986) found pyrogastrone more effective than treatment with a carbenoxolone-free version of the medication (similar to Gaviscon®) for symptom improvement and maintenance of esophageal healing. In a single blind RCT, healing rates were similar for either pyrogastrone or cimetidine (an H2 Blocker). (Maxton, 1990)

MYRTLE (*MYRTUS COMMUNIS*) EXTRACT

One small (N=45) 2016 double blind RCT demonstrated that 1000 mg of myrtle berry aqueous extract taken daily decreased symptoms although not clinically as much as 20mg of omeprazole for patients with uncomplicated GERD. Both groups improved to a statistically significant degree. Although the omeprazole performed better at 4 weeks (dropping the Frequency Scale of Symptoms of GERD 19.9 points versus 9.8 points), the difference in benefit between the groups did not reach statistical significance. (Zohalinezhad 2016) Besides the small number of subjects, study limitations include unclear concealed allocation and 3 drop outs with no intention to treat analyses.

ALOE VERA SYRUP

A small (N=79) randomized, open-label, 3-pronged pilot study compared 10ml of an aloe vera syrup to 20mg of omeprazole (once a day) and to 150 mg of ranitidine (in the morning and 30 minutes before bed). At 2 and 4 weeks of care, all of the treatment arms had statistically significant effect over baseline, although aloe vera was only about half as effective at reducing the frequency of heartburn as the other two groups (reducing frequency 29.4% compared to 62.5% for omeprazole and 52% for ranitidine). (Panahi 2015)

ADDITIONAL SUPPLEMENTS

A 2006 single blind RCT (N=351) reported complete resolution of symptoms in 100% of the patients taking a combined dietary supplementation of melatonin, vitamins and amino acids for 40 days compared to 65.7% taking 20 mg omeprazole. The difference between groups was statistically significant and the results held up under both per protocol and intention to treat analysis. Sixty subjects from the omeprazole group who did not receive satisfactory symptom relief crossed over to 40 days of the supplement and all of them achieved relief. The supplements were compounded into a single capsule composed of melatonin (6mg), tryptophan (200 mg), vitamin B12 (50 mcg), methionine (100 mg) vitamin B6 (25 mg) betaine (100mg) and folic acid (10 mg). The method of randomization and allocation concealment was not described. (de Souza 2006)

Melatonin, a key ingredient in the study above, also appeared to be effective in treating functional dyspepsia (aka "indigestion" without organic disease). One GERD RCT (N=60) comparing 5mg of melatonin in the evening to placebo reported that 56.6 % of the melatonin patients experienced complete symptom relief, and another 30% got partial relief compared to 6.7% of the placebo group.(Klupinska 2007) However, past infection with H pylori decreased this benefit. Melatonin has few side effects; relative contraindications include autoimmune diseases, pregnancy and nursing.(Werbach 2008) It can cause drowsiness so it should be taken 30-60 minutes before bedtime.

Limited evidence also supports the use of Betaine hydrochloride, digestive enzymes, bile salts and probiotics for non-ulcer (functional) dyspepsia. While there are no studies of these supplements in the treatment of GERD patients, consideration of use may be given to optimize digestive function after symptom resolution from pharmaceutical management.

5) Additional Potential Interventions

ACUPUNCTURE

A small (N=30) 4-week comparative effectiveness trial compared acupuncture plus a PPI to the standard approach of doubling the PPI dose in patients with recalcitrant GERD. The PPI plus twice-weekly acupuncture group decreased the mean daytime heartburn, night-time heartburn, and acid regurgitation scores compared to baseline and compared to the double dosed PPI group. The benefits were both clinically and statistically significant. (Dickman 2007)

ADDRESSING BREATHING MECHANICS

There is evidence that the crural portion of the diaphragm functions as an external esophageal sphincter and enhances the barrier preventing reflux of gastric contents. (Shafik 2006) Patients with GERD may have decreased diaphragm function, including a decrease in lower esophageal sphincter pressure during thoracic breathing. Sphincter pressure was demonstrated to improve (from a baseline of 7mm/Hg to 42.32mm/Hg) in some patients by means of abdominal breathing. It is theorized that practicing diaphragmatic breathing may be beneficial for these patients.(Bitner 2012)

PHARMACEUTICAL MANAGEMENT

Treatment options include proton-pump inhibitors, H_2 blockers and antacids. First line pharmaceutical treatment of GERD consists of using PPIs to decrease the acidity of the gastric juices. This can be done alongside lifestyle modifications or if lifestyle changes alone are not effective at relieving symptoms.

1) Proton Pump Inhibitors (PPIs)

PPIs are considered first line treatment for GERD due to superior efficacy at relieving heartburn compared with H_2-receptor antagonists and other medications (AGA Grade A, level 1 evidence). Nonetheless, 30-40% of patients taking PPIs experience incomplete heartburn relief. Inadequate symptom control is more common in patients with extra-gastrointestinal symptoms of GERD such as chronic cough, asthma, or laryngeal symptoms, those with long-standing symptoms, and patients with a hiatal hernia. (Katz, 2013) Multiple studies have also been conducted to try and determine which patients are most likely to respond to PPIs. A multicenter Danish trial of 471 patients found that nighttime symptoms, absence of nausea, and use of antacids or H_2 antagonists in the previous month by average-weight to overweight patients significantly increased response to omeprazole.(Meineche-Schmidt, 2000)

Standard PPI dosing

PPIs can be procured through prescriptions or over the counter (OTC). Currently, omeprazole (Prilosec), lansoprazole (Prevacid), esomeprazole (Nexium 24HR) and omeprazole/sodium bicarbonate (Zegerid) are the PPIs available OTC. The chart below gives the equivalent, recommended starting doses for PPIs.(Dynamed, UpToDate, Epocrates 2016) Neither the speed of initial symptom relief nor the chances of achieving complete relief at 4 weeks appears to differ among equivalent doses of PPIs for the treatment of non-erosive GERD (Evidence rating A). One meta-analysis concluded that high doses of esomeprazole were slightly superior to other PPIs in healing erosive GERD at eight weeks (absolute risk reduction = 4%) with a high number needed to treat (NNT = 25). (Grainek 2006) This is likely due to the fact that erosive esophagitis is present in a minority of patients who undergo endoscopy for GERD (23% of participants in one study). (El-Serag 2004)

GENERIC NAME	BRAND NAME	ADULT ORAL DOSE
Omeprazole (OTC)	Prilosec	20-40mg
Lansoprazole (OTC)	Prevacid	30mg
Pantoprazole (Rx)	Protonix	20-40mg
Rabeprazole (Rx)	Aciphex	10-20mg
Esomeprazole (OTC)	Nexium	20-40mg
Dexlansoprazole (Rx)	Dexilant	30mg

Dosing recommendations

- Take 1 pill (see chart for actual dose) 30-60 minutes before the first meal of the day (or before the last meal if night symptoms predominate).
- Treat for 8 weeks.
- If there is complete relief, begin tapering off by lowering the dose (do not stop abruptly).

If choosing to recommend that a patient take an over the counter PPI, once daily treatment with a PPI for 8 weeks is a reasonable initial trial period to treat GERD symptoms (the suggested length varies some depending on the source but most fall into the range of 4-12 weeks of treatment).(Aanen 2006; Katz 2013; Anderson 2015) Omeprazole and lansoprazole should be dosed 30-60 minutes before a meal for maximum efficacy. It has been suggested that taking the PPI prior to the first meal of the day is ideal (ACG Strong recommendation based on moderate quality evidence).(Dynamed 2016) If the patient reports complete relief of GERD symptoms on once daily treatment, you should begin tapering to a lower dose, rather than abruptly stopping the PPI, after the full 8 weeks of treatment.

Refractory symptoms

For patients who are not adequately responding to the initial dose of PPI, consider using a higher dose (double the starting dose) and/or switching from once daily to twice daily dosing. In one study, however, only 20%–25% of the PPI-failure patients demonstrated significant improvement in their symptoms after doubling the PPI dose.(Fass 2000)

A change to a different PPI if the initial choice was ineffective is another option, supported by one RCT.(Fass 2006) Providers should stress compliance with taking the medication every day and the importance of taking the medication as prescribed, 30 to 60 minutes before meals. Noncompliance with the regimen is another reason PPI treatment may fail to relieve symptoms.

Some patients with significant nighttime reflux symptoms may benefit from omeprazole/sodium bicarbonate (Zegerid) or a Histamine$_2$-receptor antagonist (aka H_2 blocker, H2RA, or H_2-receptor antagonist). Omeprazole/sodium bicarbonate (starting dose 20mg/1100mg) is effective in controlling nighttime pH when administered at bedtime instead of using a pre-meal PPI. Or a bedtime H_2 blocker can be added to the daily PPI medication regimen as it has also been shown to improve pH control overnight. H_2 blockers may decrease the prevalence of neutral breakthrough pain, but may not reduce overall symptoms. If given at bedtime, it is recommended that H_2 blockers be given on an as needed basis. (Katz 2013) ***It is important to remember that both PPIs and H_2 blockers need to be weaned whenever stopping them or the patient can get rebound acid hypersecretion.***

2) H_2 blocker Dosing

In addition to being used to treat refractory nighttime reflux symptoms, H_2 blockers may be considered as a step-down treatment for patients with GERD (as long as the patient does not have evidence of erosive disease in the esophagus). Step-down therapy would be appropriate as the next phase of treatment in a patient who has experienced relief of GERD symptoms on an eight-

week course of PPIs and is ready to try a medication with less acid suppressive action. Recommendations for dosing of H_2 blockers is as follows:(Dynamed; UpToDate; Epocrates 2016)

DRUG	Adult Oral Dose
Cimetidine (Tagamet)	400 mg twice daily
Famotidine (Pepcid)	20 mg twice daily
Nizatidine (Axid)	150 mg twice daily
Ranitidine (Zantac)	150 mg twice daily

A common approach is to use one of the above H_2 blocker regimens for 4 weeks (after an 8 week course of PPI treatment). The practitioner would then continue weening the patient off of H_2 blockers as long as GERD symptoms do not recur. If heartburn and/or regurgitation symptoms return after discontinuing acid suppression therapy, it is generally recommended to use medication on an as needed basis to control intermittent symptoms.

Adverse effects of H_2 blockers:

H_2 blockers are largely considered to be safe medications with low risk for adverse effects. However, some studies do show an increased risk of developing pneumonia with H_2 blocker use (the increased risk is also present with PPI use).(Dynamed 2016, Eom 2011) Thus, it may be reasonable to avoid use of acid suppressing drugs in a patient already at increased risk of developing pneumonia.

H_2 blockers are rated as a category B drug for pregnancy indicating there is no evidence of adverse effects on the fetus but not enough data to definitively qualify them as safe. PPIs are category C.*

3) Antacids

Antacids, such as OTC calcium carbonate (Tums) may be helpful in the short term for quick relief of intermittent GERD symptoms (level 2, midlevel evidence). (Dynamed) They are generally considered to be as effective at neutralizing acidity and improving symptoms when compared to H_2 blockers and PPIs. However, antacids are not a mainstay treatment for GERD due to the short duration of treatment effect, usually 30-60 minutes for Tums. This makes them an impractical solution for chronic reflux. In addition, some antacids also contain aspirin which can increase the risk of serious bleeding events especially in patients who drink 3 or more alcoholic beverages a day, are

* FDA pregnancy categories
A - adequate well-controlled studies failed to demonstrate risk
B - risk unlikely (animal studies failed to show risk or adverse effects, but controlled human 1st trimester studies not available/do not confirm; no evidence of 2nd/3rd trimester risk)
C - risk cannot be ruled out (animal studies show adverse effect, but no controlled human studies OR no human or animal studies)
D - positive evidence of risk (maternal benefit may outweigh fetal risk in serious or life threatening situations)
X - contraindicated in pregnancy (positive evidence of serious fetal abnormalities in human or animal studies or both)

taking NSAIDs, are over 65, have a history of stomach ulcers or bleeding problems, or are taking an anticoagulant or steroid medicine.

GERD Maintenance Medical Treatment

If a patient has recurrence of symptoms after PPIs are tapered off, PPI treatment should be resumed (ACG strong recommendation, moderate quality evidence). Maintenance therapy on PPIs is recommended in these patients and for patients with erosive esophagitis (diagnosis based on endoscopy) because of the dangers of uncontrolled long-term reflux (ACG conditional recommendation based on low quality evidence; AGA Grade A). Having uncontrolled GERD symptoms increases the risk for esophageal erosions, esophageal stricture, Barrett's esophagus and cancer and so the condition must be managed over many years by one method or another. ***Note: This becomes an important patient education message!***

Long-term GERD therapy should be given at the lowest effective dose, including the options of as needed dosing or giving medication in intermittent intervals (ACG strong recommendation, moderate quality evidence; AGA Grade A, level 1 evidence). International recommendations provide further guidance regarding frequency of GERD reassessment in patients on a maintenance regimen. The Canadian Association of Gastroenterology recommends attempting to stop or reduce the treatment dosage at least once a year (Choosing Wisely Canada 2014, Oct 29). The Royal Australian College of General Practitioners has similar recommendations.

For patients who do respond to PPIs, PPIs are considered more effective for maintenance GERD treatment than H_2 blockers [level 2 evidence]. However, a practitioner could consider step down maintenance therapy with H_2 blockers *after* successful remission of symptoms if there is no evidence of erosive esophagitis (ACG).

Potential adverse effects & complications associated with long-term PPI use

Summary of adverse effects

- Hypomagnesemia
- Vitamin B12 Deficiency
- C. difficile Infection
- Cardiovascular Disease
- Hip Fracture
- Decreased Serum Iron
- Dementia

Side effects associated with the use of PPIs are uncommon but may include headaches and diarrhea. In addition, two studies found a 29% to 39% increased risk of community-acquired pneumonia in patients using PPIs. (Giuliano 2012; Hermos 2012) Short-term use (30 days or less) may be associated with a higher risk compared with long-term use. (Giuliano 2012)

Adverse effects associated with H_2 blocker use may include gynecomastia, liver function abnormalities, hypersensitivity reactions, and cytopenias (rare).

Studies suggest PPIs carry a number of additional potential adverse effects. They may increase the risk of hypomagnesemia, vitamin B_{12} deficiency, and Clostridium difficile infection. (Ament 2012) Whether or not PPI use is associated with an increased risk of adverse cardiovascular events remains controversial. Increased risk of osteoporosis and fractures have also been looked at as potential adverse events in patients with long term use of PPIs but evidence for these complications is inconsistent.

Hypomagnesemia. A large retrospective, cross-sectional analysis in an ambulatory population found an increased incidence of hypomagnesemia and identified cases of severe hypomagnesemia in patients who had been treated with a PPI in the four months before testing (OR = 3.79; 95% CI, 2.99 to 4.82). (Markovits 2014) The clinical significance of this finding is uncertain but periodic screening of magnesium levels may be warranted.

Vitamin B_{12} Deficiency. A large case-control study indicated an increased risk of vitamin B_{12} deficiency in patients treated with PPIs (OR = 1.65; 95% CI, 1.58 to 1.73).(Lam 2013) Routine screening for B_{12} deficiency in all patients on long term PPI treatment is not recommended; however, patients *with symptoms* suggestive of vitamin B_{12} deficiency, especially elderly patients or those with H-pylori infection, should be tested. An emphasis on a healthy diet with sufficient B_{12}-fortified foods is recommended to decrease the risk of B_{12} deficiency. In addition, a multivitamin supplement may be appropriate for adults over the age of 50 because some have trouble absorbing B_{12}.

C. *difficile Infection*. PPI use may increase susceptibility to C. *difficile*. In one systematic review, 17 of 27 studies showed an increased risk (risk ratio = 1.2 to 5.0). (Bavishi 2011) However, data are conflicting on the increased risk of recurrent C. *difficile* infection when PPIs are used during treatment. In one retrospective cohort study using Veterans Administration data, the risk of recurrent infection after initial treatment was increased by 42% in patients who received PPIs during the course of treatment (OR = 1.42; 95% CI, 1.11 to 1.82).(Linsky 2010) However, in another RCT reviewing inpatient treatment of C. *difficile* infection, there was no increased risk of recurrence (hazard ratio = 0.82; 95% CI, 0.58 to 1.16).(Freedberg 2013) Pros and cons of PPI use should be weighed carefully in deciding whether or not to use PPIs in a patient at risk for C. *difficile* infection.

Cardiovascular Disease. Controversy over whether or not PPI use increases the risk of adverse cardiovascular events in patients with coronary artery disease is ongoing. In particular, research has focused on the potential increased risk among patients also taking clopidogrel - a medication prescribed to inhibit blood clot formation. In the 2013, U.S. gastroenterology guidelines concluded and gave a strong recommendation that "PPI therapy does not need to be altered in concomitant clopidogrel users as clinical data does not support an increased risk for adverse cardiovascular events." (Katz 2013) The guidelines were based on a high level of evidence.

However, Stanford University published a data mining study in 2015 that involved review of 16 million clinical documents on 2.9 million patients that suggests there is an increased risk of myocardial infarction (MI) with proton pump inhibitor use. The analysis indicated a "1.16 fold increased association (95% CI 1.09-1.24) with MI and two-fold (HR = 2.00; 95% CI 1.07-3.78; P = 0.031) increase in association with cardiovascular mortality" that was independent of clopidogrel

use. (Shah 2015) Two recently published systematic reviews also support an increased risk of adverse cardiovascular events in patients who take PPIs.(Niu 2016; Sun 2016)

Hip Fracture. An FDA warning associated PPI therapy with increased risk of hip, wrist, and vertebral fracture for patients who are at high risk for fractures. (FDA Drug Safety Communication 2013) The evidence for this association is conflicting. Several observational studies found a modest association between long-term PPI use and increased risk of hip fractures. (Kaye 2008; Gray 2010)

A recent large case-control study, however, found that those at risk of hip fracture were receiving higher doses of PPIs, and that the increased risk was confined to those with at least one additional risk factor (OR = 1.41; 95% CI, 1.21 to 1.64).(Corley 2010) In addition, a cross-sectional study evaluated patients taking PPIs over a 5 year period using the Manitoba Bone Mineral Density Database. They compared patients with hip or lumbar spine osteoporosis to controls with normal bone mineral density and found that PPI use was not associated with increased osteoporosis of the hip (OR = 0.84; 95% CI = 0.55–1.34) or the lumbar spine (OR = 0.79; 95% CI = 0.59–1.06).(Targownik 2010) However, a 2016 meta-analysis reported a moderate increase in risk of hip fracture (RR = 1.26, 95 % CI, 1.16–1.36), risk of spine fracture (RR = 1.58, 95 % CI 1.38–1.82) and any-site fracture (RR = 1.33, 95 % CI 1.15–1.54). (Zhou 2016) Currently there are no randomized controlled trials to further assess this possible connection. Guidelines indicate that it is reasonable for a patient to continue long-term PPI use when needed unless the patient has additional risk factors for hip fracture. (Katz 2013)

***Decreased Serum Iron*.** Long-term use of PPI therapy in adults may interfere with the absorption of several micronutrients such as calcium, B12, vitamin C, vitamin D, and iron. (McColl 2009) Absorption of serum iron in particular can be impacted by low HCL. Hemoglobin levels are more likely to be at least 1.0 g/dL lower in adults using PPI therapy (OR = 5.03 [95% CI, 1.71–14.78, *P* = 0.01]). Similarly, a 3% drop in hematocrit is approximately five times more likely in patients taking PPIs compared with patients taking other medications (OR = 5.46 [95% CI, 1.67–17.85, *P* = 0.01]). (McColl 2009) Monitoring serum iron should be considered for adults receiving PPI therapy.

Dementia. In one large prospective cohort study of subjects > 75 years old, those regularly taking PPIs (N=2950) were more likely to be later diagnosed with dementia (hazard ratio 1.44 [95% CI 1.36-1.52]). (Gomm 2016)

SURGERY

Surgery should be reserved for patients with contraindications to PPI therapy, patients who respond adequately to PPIs but do not wish to remain on longterm treatment (ACG strong recommendation based on high quality evidence and; AGA Grade A evidence) or whose symptoms respond to PPIs, but remain poorly controlled despite lifestyle changes and maximal PPI doses. (Katz 2013) Surgery is NOT recommended for patients who do not respond to PPIs (ACG strong recommendation based on high quality evidence).

A five-year, randomized, open parallel group trial compared long-term esomeprazole use with laparoscopic anti-reflux surgery. The authors found a clinically significant difference in symptom

remission rates: 92% (90% CI, 89% to 96%) in the esomeprazole group vs. 85% (95% CI, 81% to 90%) in the surgery group. The NNT = 14 (P = .048). (Galmiche 2011, Melvin 2011)

Step 6. Prognosis issues regarding long term care

Prognosis varies in regards to the percentage of patients who achieve complete symptom relief with PPI therapy for GERD depending on whether the patient has non-erosive GERD (no evidence of esophageal mucosa damage) verses erosive GERD (esophageal mucosa injury present on endoscopy). Studies suggest that complete symptom relief occurs in 50-60% of patients with non-erosive GERD and 70-80% of patients with erosive GERD.(Katz 2013) It is estimated that overall 40% of patients with GERD do NOT have complete symptom relief even when medication is maximized. (Kahrilas 2013) Partial or no response to medication is more likely for acid regurgitation and atypical GERD symptoms than for heartburn.(Kahrilas 2013)

The pros and cons of treatment must always be carefully weighed for a given patient to assure that PPI treatment is beneficial. Despite the potential complications of long term PPI use already discussed, an initial trial of medical treatment with PPIs remains the standard of care in the majority of patients with GERD. This is because esophageal injury associated with untreated GERD can be even more problematic with complications typically progressing along a spectrum from minor to severe: GERD esophagitis > stricture formation > Barrett's esophagus > adenocarcinoma. The majority of patients have a very good prognosis in terms of both quality of life and low risk for serious complications when appropriately treated for GERD.

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Additional sources

American Gastroenterological Association website - http://www.gastro.org

Dynamed 2016
Epocrates 2016
UpToDate 2016

APPENDIX A: GERDQ

Questions

For each question, tell us over the last week, how many times did you have each of the following symptoms.

	0 days	1 day	2-3 days	4-7 days
How often did you have a burning feeling behind your breastbone (heartburn)?	**0**	**1**	**2**	**3**
How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	**0**	**1**	**2**	**3**
How often did you have pain in the center of the upper stomach?	**3**	**2**	**1**	**0**
How often did you have nausea?	**3**	**2**	**1**	**0**
How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	**0**	**1**	**2**	**3**
How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take (such as Tums, Rolaids, Maalox?)	**0**	**1**	**2**	**3**

Interpretation

1. Total score of 0-2 points: Likelihood of GERD: 0%
2. Total score of 3-7 points: Likelihood of GERD: 50%
3. Total score of 8-10 points: Likelihood of GERD: 79%
4. Total score of 11-18 points: Likelihood of GERD: 89%

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APPENDIX B: Licorice (*Glycyrrhiza glabra)*

Dosage and Administration

- *Deglycyrrhizinated licorice (DGL) preparation (4:1 concentration): 380-760 mg TID chewed before meals*
- *Dried powdered root: 2500-5000 mg TID (not clinically tested)*
- *Fluid extract: 15 ml TID (not clinically tested)*

Contraindications

Pregnancy, lactation, liver and severe kidney disorders, according to German Commission E.

Side Effects

Glycyrrhizin content in large amounts can produce pseudoaldosteronism with resulting risks of elevated blood pressure, electrolyte disturbance, and cardiac problems. [(Stormer 1993, Crean 2009)] *Deglycyrrhizinated licorice (DGL) preparations do not pose these risks.*

Interactions with Other Botanicals and Drugs

Licorice

May influence the activity of corticosteroid drugs. [(Chen 1990, Kumagai 1967)] May add to the hypokalemic effects of thiazide and loop diuretics, [(Shintani 1979)] and may increase risk of digitalis toxicity.

DGL

Human fecal blood loss induced by 975 mg aspirin orally three times a day was less when 350 mg deglycyrrhizinated liquorice was given with each dose of aspirin. [(Rees 1979)]

Use During Pregnancy and Lactation

Contraindicated according to German Commission E.

Clinical Research Evidence

- Successful use of DGL licorice against peptic ulcer disease, as well as topical use for apthous ulcers in the mouth, [(Rees 1979, Moghadamnia 2009)] suggest that DGL might also help esophageal lesions related to GERD.
- Pyrogastrone is a medication containing carbenoxolone, a derivative of glycyrrhizin, in combination with antacid and alginate. A double blind trial [(Reed 2008)] and a DB-RCT [(Young 1986)] found pyrogastrone more effective than treatment with a carbenoxolone-free version of the medication (similar to Gaviscon®) for symptom improvement and maintenance of esophageal healing. In a single blind RCT, healing rates were similar for either pyrogastrone or cimetidine. [(Maxton 1990)] However, licorice or DGL itself remains unexamined as a treatment for GERD.

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http://www.natlife.com/. See Chewable DGL Licorice