Medical Management of GERD

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Introduction

Prior to considering surgical therapy for the management of GERD, one must consider the medical options, for which there are many. This chapter aims to give a broad overview of the medical options available to the treating physician. Prior to pursuing therapy, it is critical to make an assessment as to the etiology of the GERD symptoms. For example, the therapy for erosive esophagitis may differ from nonerosive reflux disease (NERD). It will also be very important to appreciate the therapeutic options for other conditions with similar symptoms, such as functional heartburn, hypersensitive esophagus, and non-acid reflux.

These therapies have several mechanisms, including decreasing intragastric pH, esophageal exposure to gastric contents, and sensitivity of the esophagus to any potential exposures.

Lifestyle and Dietary Interventions in the Management of GERD

The cornerstone of therapy for GERD, regardless of the etiology, is lifestyle and dietary modifications. These modifications include weight management, exercise, tobacco cessation, minimizing alcohol, and dietary modifications [1].

Weight loss is strongly recommended in patients with a BMI (body mass index) > 25 or patients with recent weight gain, in order to improve GERD

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symptoms [2–4]. Obesity has been demonstrated to be an independent risk factor for GERD. The pathophysiological mechanisms for the increased risk include lower esophageal sphincter abnormalities, increased risk of hiatal hernia, and increased intragastric pressure [5]. One cross-sectional study demonstrated that obese participants were 2.5 times more likely to have reflux symptoms or esophageal erosions compared to participants with a normal (<25) BMI [6]. A similar study demonstrated that in patients with GERD, elevated BMI was associated with more severe and more frequent reflux symptoms and esophagitis [7].

Dietary modifications can be vital in the management of GERD and reflux symptoms. While the data supporting the recommendations is not particularly strong, selective elimination could be considered for patients who can correlate their symptoms with a particular food or beverage item. Food items that have historically been targeted for avoidance include chocolate, citrus, tomato-based products, peppermint, caffeine, spicy foods, carbonated beverages, and onion [1]. Other lifestyle modifications include avoiding large meals, decreased fat intake, and elevation of the head of the bed [8]. Most importantly, avoidance of recumbency within 2–3 h of meals has been shown to decrease nocturnal gastric acidity and nocturnal GERD symptoms [9, 10].

Tobacco cessation may result in improvement of GERD symptoms [11]. One recent study evaluated the effect of smoking cessation on GERD symptoms in patients who were treated with varenicline (a nicotinic receptor partial antagonist that is used to aid in smoking cessation) before and 1 year after smoking cessation. Patients who were treated with varenicline were asked to complete a self-reported questionnaire that detailed their smoking history and GERD symptoms. In the patients who were able to successfully achieve smoking cessation, 43.9% had improvement in their GERD symptoms compared to 18.2% in the patients who did not achieve smoking cessation.

A summary of the lifestyle and pharmacologic management of GERD is summarized in Table 11.1.

Medication Management of GERD

Medical management of GERD focuses on raising intragastric pH, promoting forward motility, and manipulating lower esophageal sphincter pressure [12]. Standard medical therapies for patients failing lifestyle modifications include antacids, sucralfate, H2 receptor antagonists, and proton pump inhibitors. Other options for GERD include prokinetics and baclofen.

Both step-up and step-down [13, 14] approaches to therapy have been proposed. The step-down approach initiates treatment with more potent antisecretory drugs and then de-escalates therapy as symptoms improve. Step-up therapy involves incrementally increasing potency of therapy until symptoms are controlled. Typically step-down therapy will result in more rapid improvement in symptoms,

Table 11.1 Lifestyle and pharmacologic management of GERD

Therapy	Pregnancy category	Use during lactation (Y/N)	Comments
Weight loss [7, 9]	–	–	Studies have shown improvement in GERD symptoms and esophageal pH
Elevation of head of bed [10–12]	–	–	Studies have shown improvement in GERD symptoms and esophageal pH
Avoidance of late night meals [13, 14]	–	–	Studies have shown improvement in nocturnal gastric acidity
Tobacco and alcohol cessation [17–19]	–	–	Studies have not shown improvement in GERD symptoms
Avoidance of chocolate, caffeine, spicy foods, citrus, carbonated beverages	–	–	No studies have been performed, but selective elimination could be considered for some patients if they can correlate improvement of their symptoms with elimination of selected food item
Antacids (calcium carbonate) [12]	Category C	Yes	–
Sucralfate	Category B	Yes	–
H2 receptor clocker: Cimetidine [12]	Category B	Yes	The American Academy of Pediatrics classified as compatible with breast feeding
H2 receptor blocker: Ranitidine [12]	Category B	Yes	–
H2 receptor blocker: Famotidine [12]	Category B	Yes	Lowest concentrations in breast milk of all H2 receptor blockers
Proton pump inhibitors (PPIs) [12]	Category B[a]	No	Studies have shown growth retardation in infant mice of lactating rats

[a]All PPIs, *except* omeprazole, are pregnancy category B. Omeprazole is pregnancy category C

whereas step-up therapy will reduce PPI use, resulting in lower costs and less adverse effects related to PPI therapy. Therefore, step-down therapy should be considered in patients with complications of GERD (such as esophagitis) or more frequent/severe symptoms.

Antacids

Antacids contain medications such as aluminum hydroxide or calcium carbonate that neutralize gastric pH. While they may provide rapid onset of relief of symptoms [15], antacids do not provide long-lasting symptom control and thus require frequent dosing. In addition, they are not effective in healing esophagitis [12]. Therefore, use of antacids is mainly limited to on-demand therapy for mild GERD symptoms.

Sucralfate

Sucralfate is a complex salt composed of sucrose sulfate and aluminum hydroxide. It inhibits the activity of the enzyme pepsin and protects against the formation of ulcers [16]. It is a topical agent that binds to the mucosal surface and promotes healing and protects from acid injury. It is very poorly absorbed from the GI tract thereby exerting its therapeutic effect through local mucosal protection [16].

Sucralfate has been shown to be, potentially, efficacious in improving reflux symptoms in patients with reflux esophagitis and nonerosive reflux disease (NERD) [17]. In a placebo-controlled trial, patients with reflux treated with sucralfate had significantly higher response compared to placebo (71% vs 29%, $p < 0.001$). However, sucralfate has a short duration of action and limited efficacy compared to PPI.

A study was performed comparing the effect of sucralfate gel versus placebo in patients with NERD [18]. A total of 141 patients with moderate to severe gastroesophageal reflux symptoms (without erosions or ulcers at endoscopy) were treated for 6 weeks in a randomized, double-blind, placebo-controlled study with either 1 g sucralfate gel BID or placebo [18]. In the sucralfate treatment group, 45% of patients reported a "good" or "excellent" overall response in their symptoms compared with 22% of patients in the placebo group [18]. This study concluded that sucralfate gel was superior in the treatment of NERD compared to placebo [18].

One randomized controlled trial compared sucralfate and ranitidine in reflux esophagitis to determine if sucralfate is an effective alternative in the treatment of reflux esophagitis [19]. A total of 49 patients with reflux esophagitis were treated for 8 weeks with either 1 g of sucralfate suspension four times daily or one 150 mg ranitidine film-coated tablet twice daily [19]. After 8 weeks of treatment, reflux esophagitis was healed in 14 (out of 22) patients in the sucralfate treatment group and 13 (out of 19) patients in the ranitidine treatment group [19]. Both forms of treatment were tolerated well and had similar positive effect on symptoms, and there were no differences in the endoscopic findings after treatment. This study concluded that sucralfate is an effective alternative treatment in the treatment of reflux esophagitis [19]. There are studies that also demonstrate that sucralfate may aid in mucosal repair and ulcer healing. Sucralfate is typically used in conjunction with other GERD medications. Because it is not teratogenic, it is also considered safe to be used in pregnancy and is classified as pregnancy category B.

H2 Receptor Antagonists

H2 receptor antagonists (H2RAs) reduce acid secretion by inhibiting the histamine-2 receptor on the gastric parietal cell, which regulates acid secretion. H2RAs provide longer duration of relief compared to antacids but have slower onset of action [20].

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are the most potent antisecretory therapy. They work by binding irreversibly to the hydrogen-potassium-ATPase pump on parietal cells, thus blocking acid secretion into the gastric lumen. In general, all PPIs should be dosed approximately 30–60 min before a meal for maximal effect and are most effective when taken at least 30 min before the first meal of the day because H-K-ATPase numbers are at their peak following a prolonged fast.

PPIs also have superior healing rates of erosive esophagitis compared to H2RAs (92.1% vs 69.9% at 8 weeks), and in a study comparing lansoprazole to ranitidine, patients on lansoprazole reported improved symptoms, including less daytime heartburn, burning in the upper abdomen, and gastroesophageal regurgitation at the end of the 8-week study period [21, 22].

Among patients with nonerosive reflux disease, a Cochrane review showed that PPI therapy is superior to both H2RAs and prokinetics for heartburn relief [23]. The relative risks for heartburn remission in placebo-controlled trials were 0.37 (95% CI 0.32–0.44) for PPI, 0.77 (95% CI 0.60–0.99) for H2RA, and 0.86 (95% CI 0.73–1.01) for prokinetics. Even among patients with typical heartburn symptoms but normal endoscopic findings, PPI remained superior to H2RA (heartburn remission RR 0.78, 95% CI 0.62–0.97), although the difference was smaller compared to patients treated empirically.

Furthermore, in patients with symptoms of GERD, but normal endoscopy findings (endoscopy-negative reflux disease/ENRD), a short course of antisecretory drugs is effective in controlling symptoms. In this group, PPIs were also superior to H2RAs (four trials), although the difference was smaller compared to studies of patients treated empirically. In the only trial comparing an antisecretory (omeprazole) with a prokinetic agent (cisapride), outcome was in favor of the PPI. No placebo-controlled trials on the efficacy of prokinetics for ENRD were identified.

In patients with erosive esophagitis, PPI therapy has superior rates of healing and decreased relapse compared to H2RA and placebo [24]. A large meta-analysis comparing PPI, H2RA, sucralfate, and placebo in erosive esophagitis confirmed superior healing with PPIs (84% +/− 11% PPI, 52% +/− 17% H2RA, 39% +/− 22% sucralfate, 28% +/− 16% placebo) [25].

There have been no significant differences in symptomatic relief among different PPIs [26]. In terms of mucosal healing of erosive esophagitis, esomeprazole demonstrated a slight increase in probability of healing erosive esophagitis (RR 1.05, 95% CI 1.02–1.08) [26]. The clinical significance of this is unclear, and typically PPIs can be used interchangeably.

The vast majority (~70–80%) of patients with GERD would be expected to respond completely to standard PPI therapy. One of the most common reasons for failure is poor compliance with dosage recommendations. It is highly recommended that providers first have a discussion with patients regarding the proper use and timing of PPI therapy before increasing dosing or considering it a treatment failure. Other risk factors for lack of symptom control despite medical therapy include longer duration of symptoms, presence of hiatal hernia, and extra-esophageal symptoms [27].

Patients with otherwise noncomplicated reflux can be managed with either on-demand or intermittent PPI therapy [13, 28]. Maintenance therapy should be considered for patients with refractory symptoms or complications such as erosive esophagitis due to the high rate of recurrence off PPI. For instance, among patients with LA grade B-C esophagitis, nearly all will relapse symptomatically by 6 months [27].

PPI therapy is highly effective, but patients should be counseled regarding potential adverse effects, which can include vitamin and mineral deficiencies, bone fractures, enteric infections, pneumonia, and cardiovascular risk with co-prescription with clopidogrel. In addition, more recent studies have shown an association between chronic PPI use and the development of dementia and chronic kidney disease.

It has been hypothesized that acid suppression therapy can reduce B12 levels. The first step in cobalamin absorption is dependent on acid and pepsin to release cobalamin from dietary proteins. Thus, reduction in intragastric acid can decrease bioavailability of B12 for absorption. However, two reviews did not show evidence of B12 deficiency in patients on chronic PPI [29, 30]. It should be noted that the elderly may be at increased risk of B12 deficiency and B12 deficiency should still be considered in this population.

Similarly, absorption of dietary iron also relies on gastric acid to dissociate iron salts from food. Conditions that decrease gastric acid such as atrophic gastritis and vagotomy have been associated with iron deficiency. However, normal subjects on PPI therapy have not been shown to develop iron deficiency [29].

Hypomagnesemia has been reported in association with PPI use [31]. Serious adverse effects of hypomagnesemia can include tetany, cardiac arrhythmias, and seizure. Based on multiple case reports, the FDA issued a warning in 2011 regarding long-term (greater than 1 year) PPI use and the risk of hypomagnesemia [32]. In about 25% of the cases of hypomagnesemia, oral magnesium supplementation was insufficient, requiring discontinuation of the PPI. Therefore, it is reasonable to monitor magnesium levels in patients expected to be on prolonged PPI or in patients who take PPI with other medications (diuretics) that lower magnesium.

Concerns have also been raised regarding risk of osteoporosis. Prior studies have shown conflicting results, but a recent prospective cohort study demonstrated that PPI use was significantly associated with a shorter time to first non-traumatic fracture (hazard ratio 1.75, 95% confidence interval 1.4–2.17) [33]. Given the significant morbidity associated with osteoporosis-related fractures, the risk of PPI use should be carefully considered in populations at risk for osteoporosis.

PPIs are also thought to be associated with increased risk of enteric infections. By decreasing gastric acidity, PPI therapy may promote growth of gut microflora. Systematic reviews have demonstrated increased risk of salmonella, campylobacter, and *C. difficile* infections for patients on PPI therapy [34]. The risks and benefits of PPI therapy should be considered carefully in patients at risk for enteric infections, especially those at risk for *C. difficile*.

The data regarding risk of pneumonia with PPI use is conflicting. A large review and meta-analysis demonstrated increased risk of pneumonia in patients

using PPIs (adjusted OR 1.27, 95% CI 1.11–1.46) in the observational studies, but this relationship was not seen with the randomized studies [35]. On the other hand, a more recently published meta-analysis did demonstrate increased risk of community-acquired pneumonia among patients on PPI therapy (OR 1.36, 95% CI 1.12–1.65) [36]. Interestingly, on sub-group analysis, short duration of use was associated with increased risk of community-acquired pneumonia, while chronic use was not. This risk associated with short-term use has also been reported in other studies [37, 38]. The mechanism behind this is unclear. Further studies are needed to better delineate the risks of pneumonia associated with PPI therapy.

Clopidogrel is a commonly used antiplatelet medication. In 2009, the FDA issued a warning regarding the possibility of increased cardiovascular events among patients taking both clopidogrel and PPI therapy, as both medications are metabolized through the CYP 2C19 pathway. These recommendations were based on in vitro studies, which demonstrated decreased inhibition of platelet aggregation by clopidogrel in combination with PPI [39]. However, clinical data does not support any evidence of increased cardiovascular events with this medication combination. An analysis of well-controlled randomized trials concluded that there was no risk of adverse cardiac outcomes [40]. In fact, there may be increased risk of bleeding complications without PPI therapy in high-risk individuals on antiplatelet therapy.

Recent population database studies have raised the concern that long-term PPI use may be associated with dementia as well as chronic kidney disease. In a retrospective population cohort study, there was an association between the use of chronic PPIs and the development of chronic kidney disease (in analysis adjusted for demographic, socioeconomic, and clinical variables, HR, 1.50, 95% CI 1.14–1.96). In addition, there was a dose-dependent risk of CKD with PPI use, with twice-daily dosing being associated with increased risk. On the other hand, there was no increase in CKD risk with H2RA [41]. At this time, more studies are needed to confirm any causative relationship between PPI use and CKD development.

A large population database analysis demonstrated an association between regular PPI use and onset of dementia (HR 1.44; 95% CI, 1.36–1.52) [42]. In mouse models, PPI therapy with lansoprazole has been associated with increased deposition of beta-amyloid, which could be a mechanism for this association [43]. Similar to the study showing association with CKD, there was no clear demonstration of a causative relationship with dementia in this study.

In a recent review by the American Gastroenterological Association, it was determined that the use of long-term PPI therapy is effective and very safe. However, given these reports regarding rare but potentially serious complications from long-term PPI use, we recommend that PPIs be used judiciously and only when indicated.

The proposed risks of proton pump inhibitors and suggested practice recommendations are summarized in Table 11.2.

Table 11.2 Summary of proton pump inhibitor therapy risks and suggested practice recommendations

Risk	Summary	Practice recommendations
Nutritional		
B12 deficiency	Very rare. Elderly and malnourished at higher risk	No need for routine screening Could be considered in elderly or malnourished
Iron deficiency	Little data that PPI contributes to clinically significant iron deficiency	No need for routine screening
Hypomagnesemia	Rare, case reports published in literature	Be aware of risks of hypomagnesemia, hypokalemia, hypocalcemia. Consider checking levels in patients if there are cardiac risk factors
Fracture risk	Inconsistent studies, more recent studies do show association with fragility fractures	No recommendation for routine bone density screening
Infectious		
Enteric infections	Increased risk of salmonella, campylobacter, *C. difficile*	Consider risk/benefit especially in patients at risk for *C. difficile*
Pneumonia	Conflicting data Most associated with short-term use	PPI should not be withheld from patients when indicated
Medication interactions		
Clopidogrel	No evidence of increased cardiovascular risk	No limitations
Other complications		
Chronic kidney disease	Association between development of chronic kidney disease and PPI use in dose-dependent relationship	Discuss risks and benefits with patient. Use lowest possible PPI dose
Dementia	Association between development of dementia and chronic PPI use	Discuss risks and benefits with patient

Prokinetics

Prokinetic medications such as metoclopramide have been shown to increase lower esophageal sphincter pressure, increase esophageal peristalsis, and increase gastric emptying [44]. There is limited data showing clinical benefit of adding metoclopramide to PPI therapy. The combination of metoclopramide in addition to H2RA has not been shown to have any incremental benefit over either agent alone [45].

Unfortunately, the routine use of metoclopramide is limited by its central nervous system side effects, including drowsiness, agitation, dystonic reactions, and tardive dyskinesia [46]. The FDA has issued a black box warning regarding risk of tardive dyskinesia, an often irreversible movement disorder, with chronic use of metoclopramide [47].

An alternative to metoclopramide is domperidone, which currently requires an application for investigation drug usage permit from the FDA and is not currently approved for GERD. Although domperidone and metoclopramide have similar efficacy in gastroparesis, they have not been compared in GERD [48]. It is important to note that while on therapy, routine EKGs are needed to monitor for prolonged QT interval, which can cause ventricular arrhythmias and sudden cardiac death [49].

Macrolide antibiotics, such as azithromycin, have been shown to reduce acid reflux in addition to their prokinetic effect. However their use is limited by tachyphylaxis [50].

Baclofen

Baclofen is another alternative therapy for refractory GERD. Baclofen works through reducing transient LES relaxations, which are an important contributor to reflux [51, 52]. Baclofen has also been shown to decrease the amount of postprandial acid and non-acid reflux events [53], nocturnal reflux [54], and belching [55].

However, baclofen is not used more widely due to such side effects as drowsiness, nausea, headaches, asthenia, and tachyphylaxis. In addition, it is not currently approved by the FDA for treatment of GERD.

Management of Gastroesophageal Reflux Symptoms in Pregnancy and During Lactation

Gastroesophageal reflux symptoms are estimated to occur in up to 50% of pregnancies [56, 57]. These symptoms are typically due to the mechanical pressure that is placed on the stomach and bowel as the uterus enlarges. There is limited data to determine if there is a hormonal correlation with GERD symptoms in pregnancy. Symptoms typically manifest in the first trimester of pregnancy and resolve after delivery [58, 59].

Treatment of GERD symptoms in pregnancy typically follows a stepwise approach (Fig. 11.1). Lifestyle modifications are recommended as first-line therapy. If symptoms persist despite lifestyle modifications, calcium-containing antacids, sucralfate, and promotility drugs (i.e., metoclopramide (pregnancy category B)) are typically recommended, followed by H2 blockers (pregnancy category B) and proton pump inhibitors (pregnancy category C) [16].

Fig. 11.1 Stepwise approach to management of GERD in pregnancy

All H2 receptor blockers are excreted in human breast milk, and the effects of these drugs are unknown on the nursing human infant [60]. One review examined available data regarding the levels of H2 receptor blockers in breast milk and found that ranitidine and famotidine are safest to use during lactation, with famotidine being preferred because of its lower concentration in human breast milk [16, 61–64]. There is no data available on the use of sucralfate during breastfeeding; however, because it is virtually unabsorbed enterally, it is considered acceptable to use while breastfeeding without precautions [16, 60, 65, 66]. Proton pump inhibitors (PPIs) are typically not recommended for use by lactating mothers. Women with severe GERD symptoms can either take PPIs and discontinue lactation or use a different class of reflux therapy [16].

NERD (Nonerosive Reflux Disease) and Non-acid Reflux Management

Nonerosive reflux disease is a subset of GERD that is characterized by symptoms of reflux without mucosal erosions on endoscopy, but with evidence of pathologic levels of reflux on pH or pH-impedance monitoring. The potential causes for symptoms in NERD are microscopic inflammation, visceral hypersensitivity, or sustained esophageal contractions [67].

PPIs have been shown to be effective in NERD. However, patients with NERD have been shown to be less responsive to PPIs than patients who have erosive esophagitis by approximately 20–40% after 4 weeks of treatment [68].

Non-acid reflux disease is a subset of GERD that is characterized by symptoms of reflux; however, there is minimal to no response to PPI treatment, nor is there evidence of pathologic acid reflux during pH testing. Therefore, acid reflux does not appear to be the underlying disorder [69]. Bile acid sequestrants and oatmeal have been used to treat reflux symptoms. However, there is little data to assess the efficacy of these modalities. Baclofen can also be an option in treating non-acid reflux [69–71].

Functional Heartburn Management

Functional heartburn is the term used to describe the symptoms of a select group of patients who have heartburn symptoms but have normal esophageal acid exposure and no correlation between rare reflux events and their symptoms [70].

Therapy for functional heartburn involves a stepwise approach to alleviating symptoms (Fig. 11.2). The first step is lifestyle modification that includes avoiding triggers and identifying psychosocial features associated with symptoms [70]. Close communication between the gastroenterologist/surgeon, primary care physician, and, sometimes, psychiatry/psychology plays an important role in this aspect of therapy. If lifestyle modifications fail to improve symptoms, patients can then be treated with acid suppression [70]. While there may be no evidence in the patients' history or objective testing for acid reflux, there is data to suggest that acid

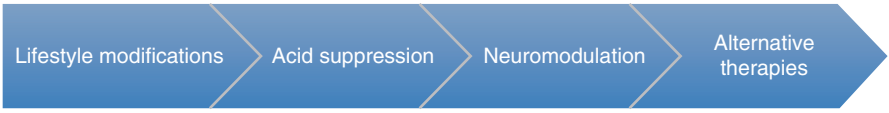

Fig. 11.2 Stepwise approach to management of functional heartburn

suppression can be beneficial in some patients with functional heartburn. This may represent the likely overlap between hypersensitive esophagus and functional heartburn [71, 72]. If acid suppression fails to improve symptoms, patients can then be treated with neuromodulatory medications that include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and melatonin [70]. If neuromodulatory therapies fail to adequately improve symptoms, patients can be treated with alternative therapies which include biofeedback, acupuncture, and esophageal-directed hypnotherapy [70].

While there is limited data to assess the effectiveness of neuromodulatory medications, one study found that imipramine (tricyclic antidepressant) did improve quality of life in patients suffering from functional heartburn; however, it did not relieve symptoms more effectively than placebo [73]. In this study, patients with established diagnoses of esophageal hypersensitivity or functional heartburn were randomized to receive either 8 weeks of imipramine 25 mg once daily or placebo [73]. The primary outcome was relief of symptoms, and the secondary outcome was improvement in the quality of life [73]. Patients receiving imipramine did not have a higher rate of satisfactory improvement in symptoms compared to patients receiving placebo [73]. Nonetheless, other trials show that tricyclic antidepressants can control esophageal pain in both healthy subjects and those that have functional esophageal disorders [74]. Thus, neuromodulatory therapy has become an important treatment modality in functional heartburn.

References

1. Nwokediuko SC. Current trends in the management of gastroesophageal reflux disease: a review. ISRN Gastroenterol. 2012;2012:391631.
2. Jacobson BC, et al. Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med. 2006;354(22):2340–8.
3. Fraser-Moodie CA, et al. Weight loss has an independent beneficial effect on symptoms of gastro-oesophageal reflux in patients who are overweight. Scand J Gastroenterol. 1999;34(4):337–40.
4. Mathus-Vliegen LM, Tytgat GN. Twenty-four-hour pH measurements in morbid obesity: effects of massive overweight, weight loss and gastric distension. Eur J Gastroenterol Hepatol. 1996;8(7):635–40.
5. Nam SY. Obesity-related digestive diseases and their pathophysiology. Gut Liver. 2016;11:323.
6. El-Serag HB, et al. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. Am J Gastroenterol. 2005;100(6):1243–50.
7. Nocon M, et al. Association of body mass index with heartburn, regurgitation and esophagitis: results of the Progression of Gastroesophageal Reflux Disease study. J Gastroenterol Hepatol. 2007;22(11):1728–31.

8. Harvey RF, et al. Effects of sleeping with the bed-head raised and of ranitidine in patients with severe peptic oesophagitis. Lancet. 1987;2(8569):1200–3.
9. Duroux P, et al. Early dinner reduces nocturnal gastric acidity. Gut. 1989;30(8):1063–7.
10. Orr WC, Harnish MJ. Sleep-related gastro-oesophageal reflux: provocation with a late evening meal and treatment with acid suppression. Aliment Pharmacol Ther. 1998;12(10):1033–8.
11. Kohata Y, et al. Long-term benefits of smoking cessation on gastroesophageal reflux disease and health-related quality of life. PLoS One. 2016;11(2):e0147860.
12. Hunt RH. Importance of pH control in the management of GERD. Arch Intern Med. 1999;159(7):649–57.
13. Inadomi JM, et al. Step-down management of gastroesophageal reflux disease. Gastroenterology. 2001;121(5):1095–100.
14. Inadomi JM, et al. Step-down from multiple-to single-dose proton pump inhibitors (PPIs): a prospective study of patients with heartburn or acid regurgitation completely relieved with PPIs. Am J Gastroenterol. 2003;98(9):1940–4.
15. Weberg R, Berstad A. Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. Scand J Gastroenterol. 1989;24(4):401–6.
16. Richter JE. Review article: the management of heartburn in pregnancy. Aliment Pharmacol Ther. 2005;22(9):749–57.
17. Wang YK, et al. Current pharmacological management of gastroesophageal reflux disease. Gastroenterol Res Pract. 2013;2013:983653.
18. Simon B, Ravelli GP, Goffin H. Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 1996;10(3):441–6.
19. Simon B, Mueller P. Comparison of the effect of sucralfate and ranitidine in reflux esophagitis. Am J Med. 1987;83(3b):43–7.
20. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology. 2000;118(2 Suppl 1):S9–31.
21. Robinson M, et al. A comparison of lansoprazole and ranitidine in the treatment of erosive oesophagitis. Aliment Pharmacol Ther. 1995;9(1):25–31.
22. Vantrappen G, et al. Omeprazole (40 mg) is superior to ranitidine in short-term treatment of ulcerative reflux esophagitis. Dig Dis Sci. 1988;33(5):523–9.
23. Sigterman KE, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2013;(5):1–84.
24. Labenz J, Malfertheiner P. Treatment of uncomplicated reflux disease. World J Gastroenterol. 2005;11(28):4291–9.
25. Chiba N, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology. 1997;112(6):1798–810.
26. Gralnek IM, et al. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol. 2006;4(12):1452–8.
27. Dickman R, et al. Comparison of clinical characteristics of patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy versus those who fully responded. J Neurogastroenterol Motil. 2011;17:387.
28. Pace F, et al. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand'. Aliment Pharmacol Ther. 2007;26(2):195–204.
29. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. Dig Dis Sci. 2011;56(4):931–50.
30. Lodato F, et al. Adverse effects of proton pump inhibitors. Best Pract Res Clin Gastroenterol. 2010;24(2):193–201.
31. Hoorn EJ, et al. A case series of proton pump inhibitor-induced hypomagnesemia. Am J Kidney Dis. 2010;56(1):112–6.
32. FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of proton pump inhibitor drugs (PPIs). 2011 [cited 2016 November 29]; Available from: http://www.fda.gov/safety/medwatch/safetyinformation/ucm258810.htm.

33. Fraser LA, et al. The effect of proton pump inhibitors on fracture risk: report from the Canadian Multicenter Osteoporosis Study. Osteoporos Int. 2013;24(4):1161–8.
34. Bavishi C, Dupont H. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. Aliment Pharmacol Ther. 2011;34(11–12):1269–81.
35. Eom C-S, et al. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. Can Med Assoc J. 2011;183(3):310–9.
36. Johnstone J, Nerenberg K, Loeb M. Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia. Aliment Pharmacol Ther. 2010;31(11):1165–77.
37. Giuliano C, Wilhelm SM, Kale-Pradhan PB. Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. Expert Rev Clin Pharmacol. 2012;5(3):337–44.
38. Hermos JA, et al. Risk of community-acquired pneumonia in veteran patients to whom proton pump inhibitors were dispensed. Clin Infect Dis. 2011;54(1):33–42.
39. Sibbing D, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. Thromb Haemost. 2009;101(4):714–9.
40. Gerson LB, et al. Lack of significant interactions between clopidogrel and proton pump inhibitor therapy: meta-analysis of existing literature. Dig Dis Sci. 2012;57(5):1304–13.
41. Lazarus B, et al. Proton pump inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016;176(2):238–46.
42. Gomm W, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol. 2016;73(4):410–6.
43. Badiola N, et al. The proton-pump inhibitor lansoprazole enhances amyloid beta production. PLoS One. 2013;8(3):e58837.
44. Champion M. Prokinetic therapy in gastroesophageal reflux disease. Can J Gastroenterol = J can gastroenterol. 1997;11:55B–65B.
45. Richter JE, et al. Omeprazole versus ranitidine or ranitidine/metoclopramide in poorly responsive symptomatic gastroesophageal reflux disease. Am J Gastroenterol. 1996;91(9):1766–72.
46. Rao A, Camilleri M. Review article: metoclopramide and tardive dyskinesia. Aliment Pharmacol Ther. 2010;31(1):11–9.
47. Reglan (metoclopramide) tablets, ODT (Orally Disintegrating Tablets), and injection. 2009 [cited 2016 November 29]; Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm170934.htm.
48. Maddern G, et al. Domperidone, metoclopramide, and placebo: all give symptomatic improvement in gastroesophageal reflux. J Clin Gastroenterol. 1986;8(2):135–40.
49. van Noord C, et al. Domperidone and ventricular arrhythmia or sudden cardiac death. Drug Saf. 2010;33(11):1003–14.
50. Rohof WO, et al. Effect of azithromycin on acid reflux, hiatus hernia and proximal acid pocket in the postprandial period. Gut. 2012;61(12):1670–7.
51. Koek G, et al. Effect of the GABAB agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. Gut. 2003;52(10):1397–402.
52. Grossi L, et al. Effect of baclofen on oesophageal motility and transient lower oesophageal sphincter relaxations in GORD patients: a 48-h manometric study. Neurogastroenterol Motil. 2008;20(7):760–6.
53. Vela M, et al. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. Aliment Pharmacol Ther. 2003;17(2):243–51.
54. Orr W, et al. The effect of baclofen on nocturnal gastroesophageal reflux and measures of sleep quality: a randomized, cross-over trial. Neurogastroenterol Motil. 2012;24(6):553–e253.
55. Cange L, et al. Baclofen-mediated gastro-oesophageal acid reflux control in patients with established reflux disease. Aliment Pharmacol Ther. 2002;16(5):869–73.
56. Ronkainen J, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. Scand J Gastroenterol. 2005;40(3):275–85.

57. Shaw MJ, et al. When does simple heartburn become a diseases? Gastroenterology. 1998;114:A284.
58. Charan M, Katz PO. Gastroesophageal reflux disease in pregnancy. Curr Treat Options Gastroenterol. 2001;4(1):73–81.
59. Anton CR, Anton E, Stanciu C. Gastroesophageal reflux disease in pregnancy. Rev Med Chir Soc Med Nat Iasi. 2001;105(1):43–7.
60. Broussard CN, Richter JE. Treating gastro-oesophageal reflux disease during pregnancy and lactation: what are the safest therapy options? Drug Saf. 1998;19(4):325–37.
61. Riley A, Crowley P, Harrison C. Transfer of ranitidine to biological fluids: milk and semen. In: The clinical use of ranitidine, Medicine Publishing Foundation Series, vol. 5. Oxford: Medicine Publishing Foundation; 1982. p. 77–86.
62. Kearns G, et al. Appearance of ranitidine in breast milk following multiple dosing. Clin Pharm. 1984;4(3):322–4.
63. Knigge UP. Histaminergic regulation of prolactin secretion. Dan Med Bull. 1990;37(2):109–24.
64. Perret G, et al. Effect of a short-term oral administration of cimetidine and ranitidine on the basal and thyrotropin-releasing hormone-stimulated serum concentrations of prolactin, thyrotropin and thyroid hormones in healthy volunteers. Pharmacology. 1986;32(2):101–8.
65. Lewis J, Weingold A. The use of gastrointestinal drugs during pregnancy and lactation. Am J Gastroenterol. 1985;80(11):912–23.
66. Hagemann TM. Gastrointestinal medications and breastfeeding. J Hum Lact. 1998;14(3):259–62.
67. Chen C-L, Hsu P-I. Current advances in the diagnosis and treatment of nonerosive reflux disease. Gastroenterol Res Pract. 2013;2013:653989.
68. Dean BB, et al. Effectiveness of proton pump inhibitors in nonerosive reflux disease. Clin Gastroenterol Hepatol. 2004;2(8):656–64.
69. Storr MA. What is nonacid reflux disease? Can J Gastroenterol. 2011;25(1):35–8.
70. Hachem C, Shaheen NJ. Diagnosis and Management of Functional Heartburn. Am J Gastroenterol. 2016;111(1):53–61; quiz 62.
71. Kavitt RT, et al. Symptom reports are not reliable during ambulatory reflux monitoring. Am J Gastroenterol. 2012;107(12):1826–32.
72. Rosen R, et al. Intraesophageal pressure recording improves the detection of cough during multichannel intraluminal impedance testing (pH-MII) in children. J Pediatr Gastroenterol Nutr. 2014;58(1):22.
73. Limsrivilai J, et al. Imipramine for treatment of esophageal hypersensitivity and functional heartburn: a randomized placebo-controlled trial. Am J Gastroenterol. 2016;111(2):217–24.
74. Prakash C, Clouse RE. Long-term outcome from tricyclic antidepressant treatment of functional chest pain. Dig Dis Sci. 1999;44(12):2373–9.