World J Surg (2017) 41:1678–1684
DOI 10.1007/s00268-017-3954-2

SURGICAL SYMPOSIUM CONTRIBUTION

Medical Treatment of Gastroesophageal Reflux Disease

Daniel A. Kroch[1] · **Ryan D. Madanick**[1]

Published online: 20 March 2017

Abstract Medical treatment is effective in the majority of patients with gastroesophageal reflux disease (GERD). Lifestyle modifications are often recommended for patients with GERD, although the data supporting lifestyle recommendations are limited. Antacids are often used to treat the symptoms of GERD, but their effect is short-lived. H2-receptor antagonists and proton-pump inhibitors provide more effective options for remission of GERD symptoms and healing of esophagitis. Prokinetic medications (e.g., metoclopramide) have not been proven to help in the control of symptoms. Baclofen, which inhibits transient lower esophageal sphincter relaxations, provide an additional option for patients with persistent symptoms related to GERD; however its use is limited by side effects. Long-term medical therapy for GERD should be tailored to each patient to provide symptomatic control and maintain esophageal mucosal healing.

Introduction

Gastroesophageal reflux disease (GERD) is a clinical syndrome that develops when the reflux of stomach contents into the esophagus, oral cavity, and/or lung causes troublesome symptoms and/or complications [1]. Heartburn, defined as a retrosternal burning sensation, and regurgitation, defined as the perception of flow of refluxed gastric contents into the mouth or hypopharynx, are the characteristic symptoms of GERD and are sufficiently descriptive to be diagnostic without endoscopy. GERD may be further classified based on the presence or absence of esophageal erosions on endoscopic evaluation as erosive reflux disease (ERD) or non-erosive reflux disease (NERD), respectively [1]. GERD-induced esophageal injury may lead to complications including esophageal stricture, Barrett's esophagus, and rarely esophageal adenocarcinoma. The spectrum of GERD-related symptoms also includes extra-esophageal manifestations such as chronic cough, hoarseness, asthma, and dental erosions [1]. The prevalence of GERD in Western societies has been estimated at 10–20%, whereas in Asia the prevalence is estimated to be less than 5% [2]. It is estimated that more than 50 million Americans experience heartburn two or more days per week [3]. The burden of GERD-related symptoms negatively affects patient quality of life, and symptoms occurring at least twice weekly have been associated with an increase in work absenteeism, a decrease in productivity and physical functioning, and low scores on sleep scales [4]. The management of patients with chronic GERD is aimed at reducing symptoms, improving quality of life, promoting healing and maintenance of healed erosive esophagitis, and preventing complications. This review will provide an overview of the current medical management options for patients with GERD (Table 1). As empiric therapy of uninvestigated GERD is much more common in the clinical setting, the

✉ Ryan D. Madanick
madanick@med.unc.edu

[1] Division of Gastroenterology and Hepatology, Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, CB #7080, Chapel Hill, NC 27599, USA

Table 1 Options for medical management of patients with gastroesophageal reflux disease

Lifestyle modifications
Tobacco cessation
Limiting alcohol
Weight loss
Elevating head of the bed during sleep
Avoiding late-evening meals
Decreasing acidic or refluxogenic foods (chocolate; fatty foods; mint; citrus; spicy foods) and beverages (coffee; caffeine; carbonation)
Pharmacologic therapy
Antacids (calcium, aluminum, magnesium, sodium salts)
Alginates[a]
Histamine-2 receptor antagonists
Proton pump inhibitors
Prokinetic agents[b]
Inhibitors of TLESRs[c]

TLESRs transient lower esophageal sphincter relaxations

[a] Marketed as a combination antacid–alginate as Gaviscon

[b] Available data do not support use of prokinetic agents in the absence of coexisting gastroparesis

[c] Baclofen is the only TLESR inhibitor currently available

following sections discuss management options for empiric therapy unless specifically noted otherwise.

Lifestyle modification (Table 2)

Lifestyle interventions are frequently the initial therapeutic approach to provide relief of mild, infrequent GERD symptoms. This approach relies on counseling patients regarding modifiable factors that can provoke or exacerbate GERD symptoms by decreasing esophageal acid exposure. These recommendations include weight loss, head-of-bed (HOB) elevation, tobacco and alcohol cessation, avoidance of late-night meals, and cessation of foods that can potentially aggravate reflux symptoms such as caffeine, coffee, chocolate, carbonated beverages, spicy foods, and foods high in acid or fat [5].

Although these lifestyle modifications are frequently recommended, the data supporting many of these recommendations are weak [6]. Despite the potential benefits of dietary modification, no studies to date have demonstrated improvement in GERD symptoms with cessation of coffee, caffeine, chocolate, spicy foods, or fatty foods [5]. Likewise, tobacco and alcohol cessation have not been shown to reduce GERD symptoms [6]. Although data suggest that carbonation lowers LES pressure, a recent systematic review found insufficient evidence to conclude that the consumption of carbonated beverages causes or exacerbates GERD symptoms [7]. Avoiding meals before bedtime can reduce supine gastroesophageal reflux, but a beneficial effect on GERD symptoms has not been demonstrated [8]. HOB elevation during sleep can improve GERD symptoms and distal esophageal acid exposure as a result of improved esophageal clearance rather than a reduction in the number of reflux events [9, 10]. The association between increasing body mass index (BMI) and GERD symptoms has been well established [11–13]. Even modest weight gain in subjects with a normal BMI has been associated with the development of GERD [11], and weight loss has been correlated with a reduction in GERD symptoms [12, 14]. A recent prospective cohort study of overweight and obese subjects demonstrated a significant reduction in GERD symptom scores in men who achieved $\geq$10% body weight loss and in women who achieved $\geq$5% body weight loss [15]. Lifestyle modifications can continue to be recommended as initial therapy for mild, infrequent GERD symptoms, but their role in moderate or severe GERD remains unproven.

Pharmacologic therapy

Pharmacologic agents for patients with persistent symptoms despite lifestyle interventions include non-absorbable agents (antacids and alginate formulations), histamine-2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs), prokinetic agents, and inhibitors of transient lower esophageal sphincter relaxations (TLESRs). The initial approach to pharmacologic therapy would ideally be based

Table 2 Effect of lifestyle modification on esophageal physiology and GERD symptoms

Factor	Esophageal acid exposure	GERD symptoms
Tobacco cessation	No effect	No effect
Limiting alcohol	No effect	No effect
Weight loss	Decreases acid exposure	Improves symptoms
Elevating HOB	Decreases supine acid exposure	Improves symptoms
Avoiding late meals	Decreases acid exposure	No effect
Altering diet	No effect	No effect

GERD gastroesophageal reflux disease, *HOB* head of the bed

on the presence or absence of reflux esophagitis; however, endoscopic evaluation of all patients with GERD symptoms is impractical and unjustifiable given its high prevalence and low morbidity [16].

Antacids

Antacids have been available over-the-counter for many years and remain frequently used to treat symptomatic GERD, despite the introduction of acid-suppressing medications [17]. Antacids comprise a group of inorganic, relatively insoluble salts of aluminum, calcium, magnesium, or sodium [18]. The previous belief that antacids work by raising the pH of gastric contents, which effectively increases the pH of the esophageal refluxate, has been challenged by more recent studies demonstrating that antacids relieve heartburn by neutralizing acid within the esophagus and exert no significant effect on intragastric pH [19]. While antacids can provide prompt and effective relief of heartburn, the effect is often short-lived. The lack of gastric acid neutralization allows repeated exposure of acidic contents to the esophagus with each subsequent reflux episode and leads to recurrent heartburn symptoms [17]. Despite their widespread use, scientific evidence supporting the use of antacids to treat GERD remains limited. Three studies in the 1980s compared antacids with placebo for the treatment of GERD [20–22]. Two studies evaluated the effect of antacids on the healing rates of esophagitis and found no improvement compared to placebo [21, 22]. Two studies found an improvement in symptoms with antacids compared to placebo, though in only one study was the effect significant [20, 21]. Antacids remain a treatment option for patients with mild, infrequent symptoms (<weekly) and may provide adjunctive benefit in patients with persistent symptoms despite acid-suppressing therapy.

Alginate

An alternative approach to acid suppression or neutralization in the treatment of symptomatic GERD is to impede the flow of refluxate into the esophagus. Symptomatic acid reflux commonly occurs after eating, despite the rise in gastric pH as a result of the buffering effect of food [23]. The recent discovery of the acid pocket, an area of relatively unbuffered, highly acidic secretion localized to the proximal stomach post-prandially, likely explains the discrepancy between the relatively high intragastric pH and low pH of refluxate observed after eating [24, 25]. Alginates are natural polysaccharide polymers that precipitate to form a low-density viscous gel of near-neutral pH on contact with gastric acid [26, 27]. The alginate gel floats on top of the gastric contents, displacing the acid pocket away from the gastroesophageal junction, and creates a mechanical barrier ("raft") to reduce reflux for up to 4 h after ingestion [28]. Imaging studies have confirmed that alginate rafts localize to the acid pocket and significantly reduce reflux compared to non-raft-forming antacids [26, 29]. Antacid formulations with alginate are significantly more likely than placebo or antacids but less likely than PPI or H2RA to achieve resolution of GERD symptoms [30]. Alginate–antacid formulations, typically marketed under the brand name Gaviscon, should be considered an alternative therapy to other antacids in patients with infrequent (<weekly), mild symptoms, especially if symptoms occur predominantly after eating, or breakthrough symptoms on anti-secretory agents.

Histamine-2 receptor antagonists, proton pump inhibitors, and prokinetics

In patients with frequent (≥weekly) or more bothersome symptoms, antacids and alginates are generally considered inadequate therapy to achieve treatment goals. H2RAs and PPIs work by decreasing gastric acid production rather than through acid neutralization or inhibition of reflux. These medications have been extensively studied in randomized controlled trials and meta-analyses for the treatment of GERD. In multiple head-to-head trials, PPIs have consistently proven superior to H2RAs in resolution of GERD symptoms, healing of esophagitis, prevention of symptom relapse at 6 months, and maintenance of symptom remission beyond 6 months [31]. A Cochrane systematic review of 32 trials with over 9700 participants found that PPI therapy was superior to H2RAs and prokinetics for the relief of heartburn in patients with non-erosive disease [32]. Meta-analyses have not demonstrated a clinically significant difference in the improvement of symptom relief between different PPIs [33]. Multiple studies have demonstrated the superior healing rates and decreased relapse rates with PPI therapy compared to H2RA or placebo for the treatment of ERD [16, 34, 35]. Given these findings, expert consensus guidelines recommend PPI therapy be used to treat all patients with erosive esophagitis [5].

While PPI therapy provides the highest level of symptom relief, healing of esophagitis, and maintenance of symptom remission, considerable controversy exists regarding the optimal initial strategy for the pharmacologic treatment of uninvestigated GERD. Proponents of a "step-up" approach suggest that beginning with less potent, less expensive medications and reserving more potent, more expensive medications if initial therapies fail, is more practical and economical [36]. In contrast, advocates of "step down" therapy argue that starting with a PPI and switching to a less expensive medication only after symptom resolution provides better prompt symptom resolution in a cost-effective

manner, with PPI-free remission rates of 50–80% without sacrificing quality of life [16, 37, 38].

Overall, PPI therapy provides symptom relief in approximately 70–80% of patients with ERD and 50–60% with NERD [5]. Multiple risk factors have been associated with lack of symptom control including presence of hiatal hernia, extra-esophageal manifestations, longer duration of symptoms, obesity, and poor medication compliance [39]. The efficacy of acid suppression with PPI therapy is influenced by the timing of administration in relation to eating, with the exception of dexlansoprazole [40]. Maximal acid suppression occurs when PPIs are taken prior to eating, optimally 15–30 min prior to a meal [41]. Despite this recommendation, a recent study found that 54% of patients used PPIs suboptimally (>60 min prior to meals, after meals, as needed, or at bedtime) [42]. Given the high rate of suboptimal PPI dosing, patients with refractory symptoms must be instructed on the optimal administration of PPIs before recommending adjustments in therapy [5]. Despite limited data to support the practice [43], switching between PPIs is commonly tried in clinical practice when symptom control is suboptimal. Increasing the frequency of PPI dosing from once to twice daily dosing in patients with refractory symptoms can result in significant symptomatic improvement; however, only a minority of patients (22–26%) achieve complete resolution of symptoms [44].

In patients with a partial response to twice daily PPI therapy, the addition of an H2RA may improve acid control by decreasing nocturnal acid breakthrough [45–47]. Considerable controversy exists regarding the duration of this effect, with studies demonstrating that tachyphylaxis to H2RA is common after 1 week of therapy [46], whereas other studies found tachyphylaxis developed in a minority (<30%) of patients after 4 weeks of combination therapy [45, 47]. The addition of bedtime H2RA therapy to daytime PPI therapy may be considered in selected patients with evidence of ongoing nocturnal reflux; however, on-demand dosing may be required in patients who develop tachyphylaxis.

Prokinetic medications theoretically improve the esophageal clearance of refluxate by augmenting esophageal peristalsis [48]. Metoclopramide, a centrally acting dopamine receptor antagonist, is the only prokinetic currently available in the USA, and increases LES pressure in healthy subjects and in patients with GERD [49]. Despite these effects, studies of metoclopramide have failed to show improvement in esophageal acid exposure, symptom control, or healing of esophagitis, either as exclusive or adjunctive therapy [50, 51]. Metoclopramide may cause CNS side effects including drowsiness, agitation, irritability, depression, dystonic reaction, and rarely (<1% of patients) tardive dyskinesia [52]. Given its lack of proven efficacy and worrisome side-effect profile, metoclopramide is currently not a recommended treatment of GERD in the absence of coexisting gastroparesis [5].

Patients with refractory symptoms despite PPI therapy warrant further investigation [5]. Those with typical esophageal symptoms should be evaluated with upper endoscopy to exclude non-reflux-related esophageal disorders, principally eosinophilic esophagitis, and to identify patients with persistent erosive disease. Not all patients with symptoms refractory to PPI therapy will have GERD, and therefore, it is important to differentiate those with persistent reflux as the etiology of ongoing symptoms from those with non-reflux-related causes. Reflux monitoring with pH or pH-impedance testing should be performed in patients who have had a negative endoscopic evaluation [5]. If pathologic acid exposure is not documented in patients who undergo testing while off anti-secretory therapy, the underlying diagnosis of GERD should be reconsidered. Patients who undergo testing while on anti-secretory therapy with evidence of ongoing reflux (acid or non-acid) and strong symptom correlation require a discussion regarding the treatment options available for refractory GERD, which may include surgical management. Detailing the rationale and interpretation of reflux testing on versus off acid suppressing therapy is beyond the scope of the current review.

Inhibitors of transient lower esophageal sphincter relaxations (TLESRs)

TLESRs are the most common mechanism of gastroesophageal reflux [53–55]. While PPI therapy significantly reduces esophageal acid exposure, PPIs do not change the absolute number of reflux episodes [56]. Persistent symptoms in patients on PPIs may result from weakly acidic (pH > 4) or weakly alkaline refluxate [56]. In these patients, further reduction of esophageal acid exposure is unlikely to occur with increased gastric acid suppression. A shift toward inhibiting TLESRs to reduce reflux may be an alternative approach to improve symptoms. Multiple neurotransmitters and receptors have been implicated in the modulation of TLESRs including γ-aminobutyric acid (GABA), metabotropic glutamate receptor 5 (mGluR5), nitric oxide, opioids, anticholinergic agents, cholecystokinin, and cannabinoid receptors of which GABA and mGluR5 appear to represent the dominant signaling pathways [57, 58]. Baclofen, a GABA-B agonist, is the only medication currently available that has demonstrated efficacy in reducing TLESRs and gastroesophageal reflux [59–61]. However, baclofen has not been found to greatly improve GERD symptoms [59, 62]. A trial of baclofen at a dosage of 5–20 mg three times daily before meals may be considered in patients with positive symptom correlation to documented reflux despite PPI therapy [5, 48]. Its use is

often limited by common side effects, including nausea, sedation, dizziness, and fatigue [48].

Summary

The initial medical management of GERD is dictated by symptom frequency and severity with treatment focused on improving symptoms and reducing complications. Patients with mild, infrequent symptoms should be counseled regarding lifestyle modification including weight loss, head-of-bed elevation, and avoidance of late-night meals. Antacids alone or in combination with alginate can provide fast symptomatic relief but are not appropriate for patients with frequent or severe symptoms. Antacid formulations containing alginate are more effective at treating postprandial symptoms than antacids alone. The mainstay of pharmacologic therapy for GERD remains acid suppression with PPIs, which provide superior symptom control and healing of erosive disease compared to H2RAs. In patients with erosive disease, PPI therapy is mandatory. Whether a "step up" or "step down" strategy is used in the initial treatment of uninvestigated GERD, maintenance therapy should use the least potent acid-suppressing regimen that controls symptoms. In patients with a partial response to PPI therapy, the addition of H2RA may be considered at bedtime if nocturnal symptoms are present. Prokinetic agents have no role in the management of GERD in the absence of coexisting gastroparesis. While there are limited options available for PPI refractory GERD, inhibition of TLESRs with the use of baclofen or surgical management may be considered in carefully selected patients. Additional studies are needed to gain further insight into the pathophysiology of GERD to discover new therapeutic targets for drug development in the future.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R (2006) The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 101(8):1900–1920 **quiz 1943**
2. Dent J, El-Serag HB, Wallander MA et al (2005) Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 54:710–717
3. Shaker R, Castell DO, Schoenfeld PS, Spechler SJ (2003) Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup survey conducted on behalf of the American Gastroenterological Association. Am J Gastroenterol 98(7):1487–1493
4. Becher A, El-Serag H (2011) Systematic review: the association between symptomatic response to proton pump inhibitors and health-related quality of life in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther 34:618–627
5. Katz PO, Gerson LB, Vela MF (2013) Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 108(3):308–328
6. Kaltenbach T, Crockett S, Gerson LB (2006) Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. Arch Intern Med 166(9):965–971
7. Johnson T, Gerson L, Hershcovici T et al (2010) Systematic review: the effects of carbonated beverages on gastro-oesophageal reflux disease. Aliment Pharmacol Ther 31:607–614
8. Piesman M, Hwang I, Maydonovitch C, Wong RK (2007) Nocturnal reflux episodes following the administration of a standardized meal. Does timing matter? Am J Gastroenterol 102(10):2128–2134
9. Johnson LF, DeMeester TR (1981) Evaluation of elevation of the head of the bed, bethanechol, and antacid form tablets on gastroesophageal reflux. Dig Dis Sci 26(8):673–680
10. Hamilton JW, Boisen RJ, Yamamoto DT, Wagner JL, Reichelderfer M (1988) Sleeping on a wedge diminishes exposure of the esophagus to refluxed acid. Dig Dis Sci 33(5):518–522
11. Jacobson BC, Somers SC, Fuchs CS et al (2006) Body-mass index and symptoms of gastroesophageal reflux in women. N Engl J Med 354:2340–2348
12. Fraser-Moodie CA, Norton B, Gornall C et al (1999) Weight loss has an independent beneficial effect on symptoms of gastro-oesophageal reflux in patients who are overweight. Scand J Gastroenterol 34:337–340
13. Nocon M, Labenz J, Jaspersen D, Meyer-Sabellek W, Stolte M, Lind T, Malfertheiner P, Willich SN (2007) Association of body mass index with heartburn, regurgitation and esophagitis: results of the Progression of Gastroesophageal Reflux Disease study. J Gastroenterol Hepatol 22(11):1728–1731
14. Mathus-Vliegen LM, Tytgat GN (1996) Twenty-four-hour pH measurements in morbid obesity: effects of massive overweight, weight loss and gastric distension. Eur J Gastroenterol Hepatol 8:635–640
15. Singh M, Lee J, Gupta N, Gaddam S, Smith BK, Wani SB, Sullivan DK, Rastogi A, Bansal A, Donnelly JE, Sharma P (2013) Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: a prospective intervention trial. Obesity 21(2):284–290
16. Labenz J, Malfertheiner P (2005) Treatment of uncomplicated reflux disease. World J Gastroenterol 11(28):4291–4299
17. McRorie JW Jr, Gibb RD, Miner PB Jr (2014) Evidence-based treatment of frequent heartburn: the benefits and limitations of over-the-counter medications. J Am Assoc Nurse Pract 26(6):330–339
18. Maton PN, Burton ME (1999) Antacids revisited: a review of their clinical pharmacology and recommended therapeutic use. Drugs 57(6):855–870
19. Decktor DL, Robinson M, Maton PN, Lanza FL, Gottlieb S (1995) Effects of aluminum/magnesium hydroxide and calcium carbonate on esophageal and gastric pH in subjects with heartburn. Am J Ther 2(8):546–552
20. Grove O, Bekker C, Jeppe-Hansen MG, Karstoft E, Sanchez G, Axelsson CK, Nielsen HO, Andersen B, Rask-Madsen J (1985) Ranitidine and high-dose antacid in reflux oesophagitis. A randomized, placebo-controlled trial. Scand J Gastroenterol 20(4):457–461
21. Weberg R, Berstad A (1989) Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis. Scand J Gastroenterol 24(4):401–406

22. Graham DY, Patterson DJ (1983) Double-blind comparison of liquid antacid and placebo in the treatment of symptomatic reflux esophagitis. Dig Dis Sci 28(6):559–563
23. Portale G, Peters J, Hsieh CC, Tamhankar A, Arain M, Hagen J, DeMeester S, DeMeester T (2007) When are reflux episodes symptomatic? Dis Esophagus 20(1):47–52
24. Thomas E, Wade A, Crawford G, Jenner B, Levinson N et al (2014) Randomised clinical trial: relief of upper gastrointestinal symptoms by an acid pocket-targeting alginate–antacid (Gaviscon Double Action)—a double-blind, placebo-controlled, pilot study in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 39(6):595–602
25. Beaumont H, Bennink RJ, de Jong J, Boeckxstaens GE (2010) The position of the acid pocket as a major risk factor for acidic reflux in healthy subjects and patients with GORD. Gut 59(4):441–451
26. Rohof WO, Bennink RJ, Smout AJ, Thomas E, Boeckxstaens GE (2013) An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. Clin Gastroenterol Hepatol 11(12):1585–1591
27. Tytgat GN, Simoneau G (2006) Clinical and laboratory studies of the antacid and raft-forming properties of Rennie alginate suspension. Aliment Pharmacol Ther 23(6):759–765
28. Hampson FC, Farndale A, Strugala V, Sykes J, Jolliffe IG, Dettmar PW (2005) Alginate rafts and their characterisation. Int J Pharm 294(1–2):137–147
29. Sweis R, Kaufman E, Anggiansah A, Wong T, Dettmar P et al (2013) Post-prandial reflux suppression by a raft-forming alginate (Gaviscon Advance) compared to a simple antacid documented by magnetic resonance imaging and pH-impedance monitoring: mechanistic assessment in healthy volunteers and randomised, controlled, double-blind study in reflux patients. Aliment Pharmacol Ther 37(11):1093–1102
30. Leiman DA, Riff BP, Morgan S, Metz DC, Falk GW, French B, Umscheid CA, Lewis JD (2017) Alginate therapy is effective treatment for gastroesophageal reflux disease symptoms: a systematic review and meta-analysis. Dis Esophagus 30(2):1–8.
31. Ip S, Chung M, Moorthy D, Yu WW, Lee J, Chan JA, Bonis PA, Lau J (2011) Comparative effectiveness of management strategies for gastroesophageal reflux disease: update. Comparative Effectiveness Review No. 29. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. HHSA 290-2007-10055-I.) AHRQ Publication No. 11-EHC049-EF. Agency for Healthcare Research and Quality, Rockville. www.effectivehealthcare.ahrq.gov/reports/final.cfm
32. Sigterman KE, van Pinxteren B, Bonis PA, Lau J, Numans ME (2013) 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 31(5):CD002095
33. Gralnek IM, Dulai GS, Fennerty MB, Spiegel BM (2006) Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol 4(12):1452–1458
34. Wang WH, Huang JQ, Zheng GF, Xia HH, Wong WM, Lam SK, Wong BC (2005) Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. World J Gastroenterol 11(26): 4067–4077
35. Peura DA, Freston JW, Haber MM, Kovacs TO, Hunt B et al (2009) Lansoprazole for long-term maintenance therapy of erosive esophagitis: double-blind comparison with ranitidine. Dig Dis Sci 54(5):955–963
36. Eggleston A, Wigerinck A, Huijghebaert S, Dubois D, Haycox A (1998) Cost effectiveness of treatment for gastro-oesophageal reflux disease in clinical practice: a clinical database analysis. Gut 42(1):13–16
37. Inadomi JM, Jamal R, Murata GH, Hoffman RM, Lavezo LA, Vigil JM, Swanson KM, Sonnenberg A (2001) Step-down management of gastroesophageal reflux disease. Gastroenterology 121(5):1095–1100
38. Tsuzuki T, Okada H, Kawahara Y, Takenaka R, Nasu J et al (2011) Proton pump inhibitor step-down therapy for GERD: a multi-center study in Japan. World J Gastroenterol 17(11):1480–1487
39. Dickman R, Boaz M, Aizic S, Beniashvili Z, Fass R, Niv Y (2011) Comparison of clinical characteristics of patients with gastroesophageal reflux disease who failed proton pump inhibitor therapy versus those who fully responded. J Neurogastroenterol Motil 17(4):387–394
40. Lee RD, Mulford D, Wu J, Atkinson SN (2010) The effect of time-of-day dosing on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR: evidence for dosing flexibility with a Dual Delayed Release proton pump inhibitor. Aliment Pharmacol Ther 31(9):1001–1011
41. Hatlebakk JG, Katz PO, Camacho-Lobato L, Castell DO (2000) Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. Aliment Pharmacol Ther 14(10):1267–1272
42. Gunaratnam NT, Jessup TP, Inadomi J, Lascewski DP (2006) Sub-optimal proton pump inhibitor dosing is prevalent in patients with poorly controlled gastro-oesophageal reflux disease. Aliment Pharmacol Ther 23(10):1473–1477
43. Fass R, Sontag SJ, Traxler B, Sostek M (2006) Treatment of patients with persistent heartburn symptoms: a double-blind, randomized trial. Clin Gastroenterol Hepatol 4(1):50–56
44. Fass R, Murthy U, Hayden CW, Malagon IB, Pulliam G, Wendel C, Kovacs TO (2000) Omeprazole 40 mg once a day is equally effective as lansoprazole 30 mg twice a day in symptom control of patients with gastro-oesophageal reflux disease (GERD) who are resistant to conventional-dose lansoprazole therapy—a prospective, randomized, multi-centre study. Aliment Pharmacol Ther 14(12):1595–1603
45. Rackoff A, Agrawal A, Hila A, Mainie I, Tutuian R, Castell DO (2005) Histamine-2 receptor antagonists at night improve gastroesophageal reflux disease symptoms for patients on proton pump inhibitor therapy. Dis Esophagus 18(6):370–373
46. Fackler WK, Ours TM, Vaezi MF, Richter JE (2002) Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. Gastroenterology 122(3):625–632
47. Mainie I, Tutuian R, Castell DO (2008) Addition of a H2 receptor antagonist to PPI improves acid control and decreases nocturnal acid breakthrough. J Clin Gastroenterol 42(6):676–679
48. Vela MF (2014) Medical treatments of GERD: the old and new. Gastroenterol Clin N Am 43(1):121–133
49. Champion MC (1997) Prokinetic therapy in gastroesophageal reflux disease. Can J Gastroenterol 11(Suppl B):55B–65B
50. Grande L, Lacima G, Ros E, García-Valdecasas JC, Fuster J, Visa J, Pera C (1992) Lack of effect of metoclopramide and domperidone on esophageal peristalsis and esophageal acid clearance in reflux esophagitis. A randomized, double-blind study. Dig Dis Sci 37(4):583–588
51. Richter JE, Sabesin SM, Kogut DG, Kerr RM, Wruble LD, Collen MJ (1996) Omeprazole versus ranitidine or ranitidine/metoclopramide in poorly responsive symptomatic gastroesophageal reflux disease. Am J Gastroenterol 91(9):1766–1772
52. Rao AS, Camilleri M (2010) Review article: metoclopramide and tardive dyskinesia. Aliment Pharmacol Ther 31(1):11–19
53. Dent J, Dodds WJ, Friedman RH, Sekiguchi T, Hogan WJ, Arndorfer RC, Petrie DJ (1980) Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. J Clin Invest 65(2):256–267

54. Dodds WJ, Dent J, Hogan WJ, Helm JF, Hauser R, Patel GK, Egide MS (1982) Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. N Engl J Med 307(25): 1547–1552
55. Mittal RK, McCallum RW (1988) Characteristics and frequency of transient relaxations of the lower esophageal sphincter in patients with reflux esophagitis. Gastroenterology 95(3):593–599
56. Boeckxstaens GE, Smout A (2010) Systematic review: role of acid, weakly acidic and weakly alkaline reflux in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 32(3):334–343
57. Kessing BF, Conchillo JM, Bredenoord AJ, Smout AJ, Masclee AA (2011) Review article: the clinical relevance of transient lower oesophageal sphincter relaxations in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 33(6):650–661
58. Dent J (2010) Reflux inhibitor drugs: an emerging novel therapy for gastroesophageal reflux disease. J Dig Dis 11(2):72–75
59. van Herwaarden MA, Samsom M, Rydholm H, Smout AJ (2002) The effect of baclofen on gastro-oesophageal reflux, lower oesophageal sphincter function and reflux symptoms in patients with reflux disease. Aliment Pharmacol Ther 16(9):1655–1662
60. Zhang Q, Lehmann A, Rigda R, Dent J, Holloway RH (2002) Control of transient lower oesophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in patients with gastro-oesophageal reflux disease. Gut 50(1):19–24
61. Vela MF, Tutuian R, Katz PO, Castell DO (2003) Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. Aliment Pharmacol Ther 17(2):243–251
62. Cossentino MJ, Mann K, Armbruster SP, Lake JM, Maydonovitch C et al (2012) Randomised clinical trial: the effect of baclofen in patients with gastro-oesophageal reflux—a randomised prospective study. Aliment Pharmacol Ther 35(9):1036–1044