A RESEARCH REVIEW™
EDUCATIONAL SERIES

The management of gastro-oesophageal reflux disease (GORD)

Making Education Easy 2020

About the expert

Alasdair Patrick
BHB, MBChB, FRACP

Dr Alasdair Patrick is a Kiwi Gastroenterologist with a passion for evidence-based, patient-focused care. He trained in the Auckland region then did a fellowship at The Royal Free Hospital in London with a focus on oesophageal disease. Dr Patrick worked as a consultant internationally in the United Kingdom and Singapore and is considered an expert in diagnostic and therapeutic endoscopy. In 2007 he returned to NZ to Middlemore Hospital. At CMDHB he has held various roles including: Director of Physician Training, Head of the Department of Gastroenterology, Head of the Bowel Screening Programme and Secretary of the National Endoscopy Accreditation committee. He is Director of the Macmurray Gastroenterology Centre in Auckland has a special interest in the areas of inflammatory bowel disease, irritable bowel syndrome, liver disease, colorectal cancer, minimally invasive technology, obesity management and GORD. Alasdair is widely published and currently actively involved in a number of clinical trials.

The review presents relevant background information on gastro-oesophageal reflux disease (GORD) and focuses on its management, including pharmacotherapy. In particular, it describes alginate-based preparations and their place in therapy: as a first-line option in patients with occasional, mild GORD symptoms, and in pregnancy and breastfeeding; for long term and/or on-demand therapy following the stepping-down or cessation of proton pump inhibitors (PPIs); and in combination with PPIs for relief of breakthrough symptoms in PPI-unresponsive GORD. This review is intended as an educational resource for health care professionals and is sponsored by Reckitt Benckiser Ltd.

Introduction

Gastro-oesophageal reflux, also called "acid reflux," occurs when the stomach contents back up into the oesophagus and/or mouth.[1] It occurs because the sphincter muscle at the lower oesophagus is designed to allow vomiting to occur as a protective mechanism. Occasional reflux is normal and can happen in healthy infants, children, and adults, most often after eating a meal.[1] Most episodes are brief and do not cause troublesome symptoms or complications.

In contrast, people with gastro-oesophageal reflux disease (GORD) experience bothersome symptoms or damage to the oesophagus as a result of acid reflux.[2]

The most common symptoms of GORD are:[3,4]

- Heartburn – This typically feels like a burning sensation in the centre of the chest, which sometimes spreads to the throat. It most often happens after a meal.
- Indigestion (dyspepsia) - Pain and discomfort felt in the lower chest or abdomen, during or after meal.

Other symptoms of GORD may include:

- Regurgitation – This is when stomach contents (acid combined with undigested food) flow back into the mouth or throat, producing an acid taste in the mouth.
- Acid taste in mouth
- Stomach pain (pain in the upper abdomen)
- Chest pain
- Difficulty swallowing (dysphagia) or pain on swallowing (odynophagia)
- Persistent laryngitis/hoarseness (due to acid irritating the vocal cords)
- Persistent sore throat or cough
- Sense of a lump in the throat.

Diagnosis and treatment of GORD

Most patients with typical symptoms of GORD do not require diagnostic testing.[5] However, in patients with alarm symptoms such as dysphagia, odynophagia, anorexia, weight loss and upper gastrointestinal bleed, upper endoscopy investigation is warranted.[5] The use of pH testing is reserved for certain clinical settings when further management is needed in patients who partially or showed complete lack of response to treatment.[5]

Treatments for GORD include lifestyle changes, over-the-counter medications, prescription medications and surgery if medication does not work or if patients do not want to take medication on a long-term basis.[6]

Smoking cessation and weight loss should be recommended to GORD patients who smoke and are obese, respectively.[7] Raising the head of the bed and avoiding late evening meals are effective in nocturnal GORD.[7]

While lifestyle modifications may be effective in reducing or eliminating GORD symptoms in some patients, the majority of patients will require pharmacological therapy.[8] Appropriate medical therapies vary with the severity of symptoms and include antacids, alginates, proton pump inhibitors (PPIs), and histamine 2 receptor antagonists (H_2RAs)* (Table 1).[8,9] An algorithm for the management of GORD in primary-care adapted from National Institute for Health and Clinical Excellence (NICE) guidelines is presented in Figure 1.

* The H_2RA ranitidine has been recalled in NZ due to possible NMDA contamination.

Table 1. Summary of therapies for GORD[17-19]

	Alginates	Antacids	PPIs	H_2RAs*
Mode of action	Prevents reflux by forming a raft on top of stomach contents	Temporarily neutralises stomach acid	Reduces stomach acid production	Reduces stomach acid production
Onset of action	Quick	Quick	Slow	Slow
Duration of action	Long	Short	Long	Long

* The H_2RA ranitidine has been recalled in NZ due to possible NMDA contamination.

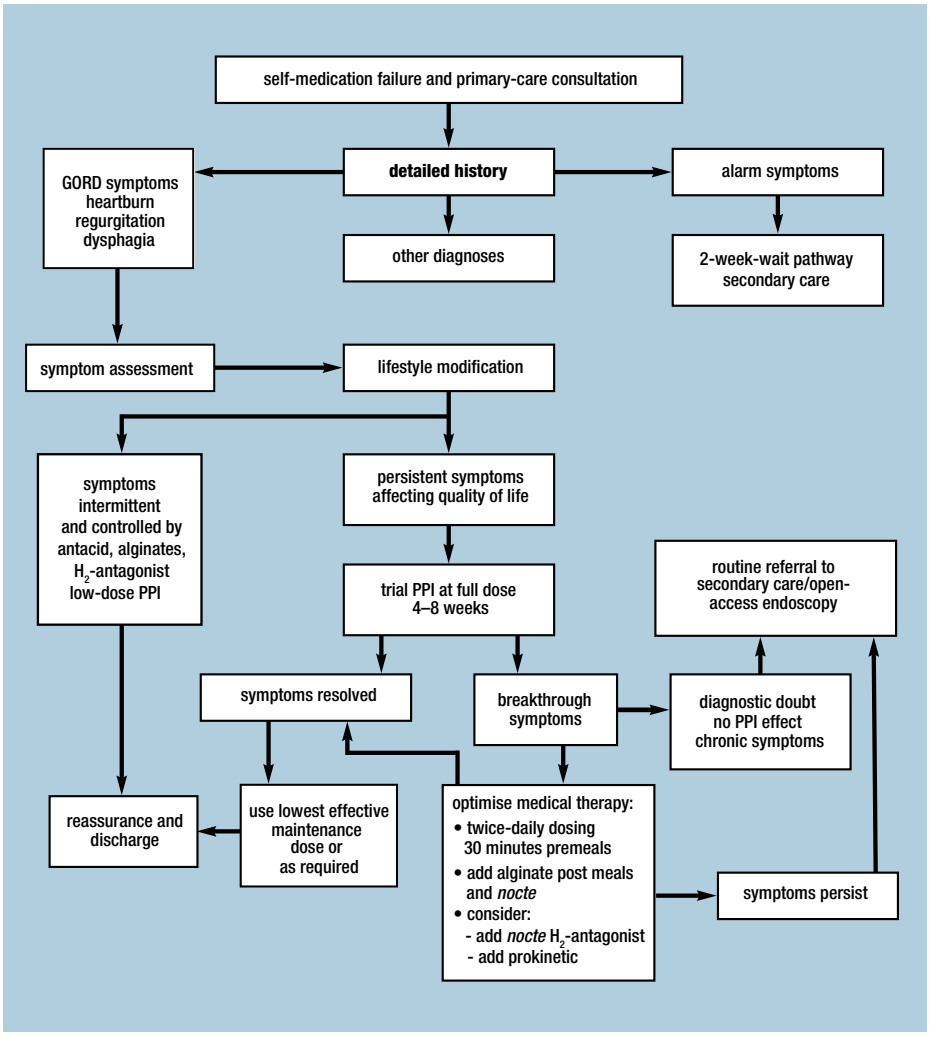
The most widely practised strategy for symptomatic GORD is reducing gastric acidity. Over-the-counter antacids are mostly used for mild symptoms; their onset of action is rapid, but their effect is short lived.[10]

In patients with moderate to severe symptoms, PPIs have become first-line therapy due to their profound and consistent acid suppression.[5,11] However, PPI therapy has limitations. Many patients have an incomplete symptom response and others, either because of general unease with taking long-term medication or because of the intermittent nature of symptoms, prefer to address reflux symptoms with as needed medication.

Patients with mild symptoms who have not responded to prescribed PPIs may be offered a H_2RA as an alternative.[12] However, the use of H_2RAs may be limited in the treatment of GORD due to sudden pharmacologic tolerance, which can occur after a single dose, and interactions with other medicines.[13,14]

Alginate-based preparations create a near neutral pH 'raft' floating on top of acidic digestive juices that settles in the region of the acid pocket, potentially offering more effective targeted therapy.[15] Alginate-based formulations offer rapid symptom relief, making them a preferred option for on-demand treatment.[16]

Figure 1. Proposed algorithm for the treatment of GORD adapted from the NICE guidelines[20]



Proton pump inhibitors

Based on current evidence, PPIs provide symptom relief in approximately 50% to 80% of patients with GORD.[5] Complete relief of heartburn with PPIs occurs at a rate of approximately 11.5 percent per week.[21] For many people, short-term PPI use (4–8 weeks) is appropriate.[22-24] PPIs can be stepped-down or 'deprescribed' in symptom-free patients starting from 4 weeks.[25] The expected duration of treatment should be discussed with patients when initiating a PPI so they are aware that it is intended for short-term use. Ongoing treatment may be indicated if symptom resolution has not been achieved or for patients with complications associated with GORD.[26]

Side effects of long-term PPI

Long-term PPI treatment is associated with a small increase in the risk of adverse outcomes, including bone fractures,[27] malabsorption of nutrients,[28-30] chronic kidney disease,[31] increased susceptibility to some bacterial infections such as *Clostridium difficile* infection,[26,32] community-acquired pneumonia[28,33] and dementia.[34] The magnitude and significance of these side effects is uncertain.

Reviewing long-term PPI use

Because PPI use is very prevalent, there are likely to be several patients who are being treated with a higher dose than is necessary or for longer than is recommended.[35] BPAC recommends that PPI use is regularly reviewed to determine whether long-term treatment is still indicated, or whether a lower dose or stopping completely could be trialled.[36]

It may be appropriate to step down or discontinue PPI treatment in some patients, such as:[25]

- Patients who have been taking a PPI for a minimum of four weeks and have had a complete resolution of their symptoms.
- When the risks associated with ongoing treatment outweigh the benefits.
- When ongoing use is not indicated, e.g. prescribed for ulcer prophylaxis and the NSAID has been stopped.

According to BPAC, long-term treatment with a PPI is indicated in some patients, e.g. for those with Barrett's oesophagus, chronic NSAID treatment or erosive, ulcerative or stricturing GORD that has been confirmed by endoscopy.[26] However, periodic review of PPI treatment is recommended in these patients to ensure that the lowest effective dose is being prescribed to manage symptoms.[26]

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC), has stated that high-dose PPIs appear to be over-prescribed, for excessively long periods of time and particularly among older people.[37]

This has resulted in restrictions being placed on the prescription of PPIs listed on the Pharmaceutical Benefits Scheme (PBS) General Schedule, as well as changes to the terminology, criteria and the number of repeats.[38]

Stepping down PPIs

A "step down" approach involves slowly reducing the dose over time before withdrawing the medicine completely.[36] Patients should be warned about possible rebound symptoms; abrupt withdrawal of a PPI can cause rebound gastric acid secretion, leading to symptoms which may be mistaken for the re-emergence of GORD and consequently the resumption of PPI use and dependence.[39]

This rebound acid secretion can be prevented by stepping down the dose over a few weeks, e.g. halving the daily dose, then taking the medicine on alternate days before discontinuing the PPI completely.[36] Some patients may require another medicine to manage their rebound symptoms, e.g. a H_2RA, antacid, or alginate-based preparations.[25] Up to 85% of patients on long-term PPI therapy for GORD could be stepped down to lower dose PPI or alginate therapy alone, leading to clinical and cost benefits.[40,41] Patients who are trialling stepping down to a lower dose or stopping PPI treatment should be reminded about lifestyle modifications to help manage the symptoms of GORD.[36]

A protocol for stepping down PPIs over two to four weeks[25,36,42]

Step 1: Establish the patient's regular PPI requirements.

Step 2: Halve the daily dose of the PPI or change the frequency of dosing, e.g. from twice daily to once daily or from daily use to alternate days. Patients who have been on a high dose may require a second or third step-down to reach the lowest dose, e.g. 10 mg on alternate days.

Step 3: Stop the PPI.

If GORD symptoms occur at any stage during the step-down process or after stopping, trial a H_2RA, or an antacid, or an alginate-based preparation.

Breakthrough symptoms on PPIs

A 2008 survey by the American Gastroenterological Society found that, despite the efficacy of PPIs, 38% of patients on once-daily PPI therapy had breakthrough symptoms.[43] Of these, 65% experienced symptoms at night.[43] Furthermore, only 23% of patients on a PPI reported that they were completely satisfied with their current therapy.[43] In a systematic review of randomised clinical trials of patients on PPIs, the prevalence of persistent troublesome heartburn was 32% and of any heartburn was 52%.[44] Indeed, the vast majority of patients who remain symptomatic on a standard (once-daily) dose of PPI will continue to experience symptoms on even higher doses of PPIs.[45]

The first step in the management of refractory GORD is optimisation of PPI therapy.[22] Patients should be reminded about the importance of taking PPIs daily in order to achieve maximum benefit.[5,9] Taking PPIs at the correct time is also key - 30 minutes prior to a meal.[5,9] Another important step in optimising PPI treatment is the continuous need to follow life style modifications.[46] Interestingly, a study has shown that splitting the PPI dose throughout the day improves control of intragastric pH.[47] However, spreading the PPI dose in this way may reduce compliance.[5]

The addition of an H_2RA at night may relieve nocturnal symptoms, but to avoid tachyphylaxis developing, a regimen of two weeks on and two weeks off is recommended.[48] Additional adjuvant therapy with an alginate preparation may be of benefit after meals and at night.[48] Changing to an alternative PPI can be trialled but the evidence for this is low.[48] Finally, other nonpharmacological methods could be considered, such as endoscopic treatment or anti-reflux surgery.[5]

Steps for optimisation of PPI therapy[5,9,48]

Lifestyle modifications
Improve compliance
Ensure proper dosing time
Split the PPI dose
Change to another PPI
Add non-PPI medication (H_2RA, alginate-based preparations)

Why do breakthrough symptoms occur on PPIs?

GORD is the result of stomach contents entering the oesophagus, where they are not as well tolerated.[49]

This is usually prevented by the lower oesophageal sphincter.[50] Transient lower oesophageal sphincter relaxations can allow the contents at the top of the stomach (the highly acidic 'acid pocket') to reflux into the oesophagus.[50,51] In fact, up to 80% of GORD episodes are caused by transient lower oesophageal sphincter relaxations.[52]

The acid pocket

A relatively new concept of the postprandial 'acid pocket' – a layer of acid pooling in the proximal stomach – explains the paradox of increased heartburn after eating despite the buffering effect of food and supports the concept of using postprandial alginate preparations to manage these symptoms.[48] The acid pocket appears due to the proximal cardia region of stomach escaping the buffering effect of meal[53] and is visible 15 minutes postprandially.[54] The presence of the acid pocket is exacerbated by hiatus hernia and reduced lower oesophageal sphincter pressure.[50]

Gaviscon: an alginate-based preparation

Gaviscon is a combination of sodium alginate and antacid. Alginate is a polysaccharide derived from seaweed. An alginate-antacid formulation creates a raft that targets the acid pocket.[15] The raft is formed by the reaction of sodium alginate with gastric acid to form an alginic acid gel. This gel floats on top of the stomach contents due to its reduced density resulting from entrapped carbon dioxide formed by the reaction of the bicarbonate in antacids with gastric acid. Unlike traditional antacids which chemically neutralize gastric acid, or H_2RAs which pharmacologically reduce acid secretion, alginate raft-forming agents appear to act primarily by a physical, rather than a chemical or pharmacological means. This unique mechanism of action provides both the rapid onset of action of conventional antacids and a longer effective duration, up to 4 hours.[16]

Kwiatek et al. demonstrated that alginates displace the acid pocket away from the oesophagogastric junction in patients with GORD.[55] Furthermore, scintigraphic analysis of patients with a large hiatus hernia revealed that an alginate-antacid preparation forms a raft within minutes of ingestion and co-localises with the acid pocket and, compared with antacids, increases subdiaphragmatic positioning of the acid pocket and decreases the number of acid reflux episodes.[15] This has clinical implications for patients with postprandial GORD, who may be able to adequately control their symptoms with alginates.[15] The acid pocket also persists after PPI treatment,[56] thus alginates may also benefit patients with insufficient response to PPIs.

Alginates for the first-line treatment of mild GORD symptoms

A 2017 systematic review and meta-analysis demonstrated that alginates (usually formulated in combination with antacids) were significantly superior at improving GORD symptoms compared with antacids alone and placebo.[57] Alginate therapy was uniformly favoured over antacids or placebo in all studies.[57] The same systemic review and meta-analysis showed that compared to PPIs or H_2RAs, alginates appeared less effective but the difference was not statistically significant.[57] The authors of the review suggested that alginate could be used as a first-line treatment for patients with mild GORD symptoms, thus reducing the need for acid suppressive therapy.[57]

Two studies compared an alginate-based preparation with omeprazole and found that the alginate-based preparation was noninferior to omeprazole for the treatment of moderate, episodic heartburn.[58,59]

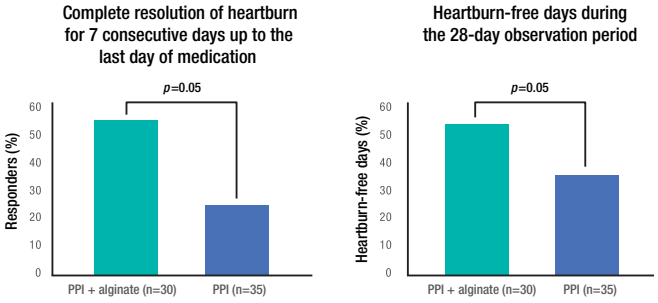
The role of alginates in the step-down of PPIs

Two studies have evaluated the efficacy of an alginate suspension in stepping down or off of PPIs.[60,61] Murie et al. showed that among patients taking an alginate suspension during the step-down/cessation of therapy, 83% successfully reduced or stopped their PPIs at the end of 1 year.[60] Similarly, Coyle et al. demonstrated that 75% of patients taking an alginate suspension stepped down or off their PPIs at 1 year.[61]

Alginates combined with PPIs in patients with severe or PPI-unresponsive GORD

A randomised controlled trial found that alginate plus omeprazole significantly increased the incidence of complete heartburn resolution compared to omeprazole alone in patients with GORD (56.7% vs 25.7%) (Figure 2).[62] The symptom frequency was at least 2 days per week during the 1-month period before entering the study.

Figure 2. Alginates as add-on treatment to PPIs in GORD[62]



Another randomised controlled trial showed that the addition of an alginate-based preparation for patients with persistent reflux symptoms despite PPI therapy significantly reduced the frequency and severity of heartburn as well as reducing the frequency of regurgitation and night-time symptoms.[63]

The results of this trial indicate that adding an alginate-based preparation, with the complementary modes of action to PPIs, offers the benefit of an additional reduction in reflux symptoms without significant adverse events.

Much of the ongoing research examines the efficacy of alginate-based preparations as add-on therapies to PPIs. This has the potential to change management strategies because it offers gastroenterologists an alternative to escalating PPI doses, which is the current standard practice.[54]

Treatment of GORD during pregnancy and breastfeeding

Between 30 – 50% of pregnant women experience symptoms of GORD.[64] Evidence from randomised controlled trials regarding the safety of GORD medications during pregnancy is scarce.[65] Available evidence from non-randomised studies suggests that the use of alginates, antacids, PPIs and H_2RAs for GORD during pregnancy presents no known significant safety concerns for either the mother or baby. In studies of alginate use in pregnancy, no particular risks have been shown for both mother and unborn baby when alginate was administered during all trimesters of pregnancy.[66] Antacids are safe for use during pregnancy and give immediate relief.[67] The use of PPIs during pregnancy is not associated with an increased risk for birth defects, miscarriage, preterm birth, or perinatal mortality or morbidity.[64,68-71] The use of H_2RAs in pregnancy is not associated with any increase in risk of miscarriage, preterm birth or small-for-gestational-age baby.[72]

Drugs having a minimal systemic effect, such as alginates, are preferred during breast feeding, but evidence from clinical trials is lacking.[73]

Surgical treatment of GORD

Candidates for surgical therapy of GORD include patients who are concerned about long-term pharmacotherapy, and patients who develop adverse events and who are unable to comply with regular, long-term medical treatment.[5] Furthermore, patients with an abnormal pH test while on maximum PPI dose, symptoms of regurgitation, large hiatal hernia and possibly those with symptoms associated with non-acid reflux, may also require surgery.[5]

Laparoscopic surgical fundoplication is the most common surgery for GORD but the rate of utilisation has been substantially decreasing in recent years.[5] Endoluminal therapies provide effective symptomatic control in a subset of patients and are a suitable alternative to medical or surgical treatment.[5] Two available endoluminal techniques are EsophyX® and Stretta.[5] The EsophyX® device, or transoral incisionless fundoplication, creates a valve at the oesophagogastric junction.[5] Stretta is an endoscopic device that uses radiofrequency energy applied to the muscles of the lower oesophageal sphincter and the gastric cardia resulting in an improvement of reflux symptoms.[74]

EXPERT'S CONCLUDING COMMENTS

GORD is a very common symptom that burdens many patients with a significant reduction in their quality of life. PPIs remain the mainstay in our treatment armament but they only reduce acid production and do not treat the actual pathology which is a poorly functioning lower oesophageal barrier. This is why at least a third of PPI users fail this treatment alone. Alginates create a short term improvement in barrier function and their use along with optimising acid control can lead to clinical improvement in some patients. Those who have alarm symptoms or who fail treatment are candidates for referral for further investigation including endoscopy and pH studies. Fundoplication is an appropriate effective option for some of these patients but many do not want surgery. There is growing evidence for the place of procedures such as Stretta but we need more options in this therapeutic gap.

TAKE-HOME MESSAGES

- Over-the-counter medications can provide relief in patients with mild GORD symptoms.
- Alginate-based preparations have a different mechanism of action to antacids.
- The acid pocket is a layer of acid pooling in the proximal stomach after a meal.
- Alginate-based preparations physically form a raft that floats on top of the acid pocket preventing acid refluxing back into the oesophagus.
- Alginate-based preprations are superior to antacids to improve GORD symptoms.
- PPIs are first line therapy for moderate to severe GORD symptoms.
- Many people taking PPIs still have persistent symptoms.
- PPI use should be regularly reviewed to determine whether treatment is still indicated.
- Rebound acid hypersecretion can occur after stopping prolonged PPI treatment.
- Alginate-based preparations work non-systemically so are also suitable during pregnancy and breastfeeding.
- Alginate-based preparations are an option for different types of reflux symptoms:
  - occasional GORD symptoms.
  - breakthrough symptoms on PPIs.
  - stepping down/off PPIs.
- Corrective antireflux surgery is an option when pharmacotherapy is unsuccessful.

REFERENCES

1. BPAC NZ. Managing gastro-oesophageal reflux disease (GORD) in adults: an update. Best Practice Journal. 2014. V61. https://bpac.org.nz/bpj/2014/june/gord.aspx
2. Ronkainen J, Agreus L. Epidemiology of reflux symptoms and GORD. Best Pract Res Clin Gastroenterol. 2013;27:325–37.
3. Kahrilas P. Patient education: Gastroesophageal reflux disease in adults (Beyond the Basics). 2019. https://www.uptodate.com/contents/gastroesophageal-reflux-disease-in-adults-beyond-the-basics/print
4. WebMD. Acid reflux symptoms. https://www.webmd.com/heartburn-gerd/guide/acid-reflux-symptoms#1
5. Sandhu DS, et al. Current Trends in the Management of Gastroesophageal Reflux Disease. Gut Liver. 2018;12:7-16.
6. NHS UK. Heartburn and gastro-oesophageal reflux disease (GORD). 2016. http://www.nhs.uk/conditions/Gastroesophageal-reflux-disease/Pages/Introduction.aspx.
7. Ness-Jensen E, et al. Lifestyle Intervention in Gastroesophageal Reflux Disease. Clin Gastroenterol Hepatol. 2016;14:175-82.e1-3.
8. Lowe RC. Medical management of gastroesophageal reflux disease. GI Motility online (2006) doi: 10.1038/gimo54.
9. Pandit S, et al. Gastroesophageal reflux disease: A clinical overview for primary care physicians. Pathophysiology. 2018;25:1-11.
10. Boeckxstaens G, et al. Symptomatic reflux disease: the present, the past and the future. Gut 2014;63:1185–93.
11. Kahrilas PJ, et al. AGAI medical position statement: management of gastroesophageal reflux disease. Gastroenterol. 2008;135:1383–91.
12. New Zealand Formulary (NZF). NZF v94. 2020. www.nzf.org.nz.
13. Dutta U, Moayyedi P. Management of reflux-related symptoms. Best Pract Res Clin Gastroenterol. 2013;27:387–400.
14. McRorie J, et al. Histamine2-receptor antagonists: Rapid development of tachyphylaxis with repeat dosing. World J Gastrointest Pharmacol Ther. 2014;5:57–62.
15. Rohof WO, et al. An alginate-antacid formulation localizes to the acid pocket to reduce acid reflux in patients with gastroesophageal reflux disease. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2013;11(12):1585–91.
16. Mandel KG, et al. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther. 2000;14(6):669-90.
17. Strugala V, et al. A Randomized, controlled, crossover trial to investigate times to onset of the perception of soothing and cooling by over-the-counter heartburn treatments. J Int Med Res. 2010;38:449-57.
18. Chevrel B. A comparative crossover study on the treatment of heartburn and epigastric pain: Liquid Gaviscon and a magnesium--aluminium antacid gel. J Int Med Res. 1980;8:300-2.
19. Nguyen L, et al. Current and Prospective Pharmacotherapies in Gastroesophageal Reflux Disease. Clin Med Ther. 2009. https://doi.org/10.4137/CMT.S2744
20. Basu KK. Concise guide to management of reflux disease in primary care. Prescriber. 2012;23:19-28.
21. Chiba N, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology. 1997;112:1798.
22. Katz PO, et al. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol 2013;108:308-28.
23. Jacobson BC, et al. Who is using chronic acid suppression therapy and why? Am J Gastroenterol 2003;98:51-8.
24. Ramakrishnan K, Salinas RC. Peptic ulcer disease. Am Fam Physician 2007;76:1005-12.
25. Farrell B, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline.mCan. Fam. Physician. 2017, 63, 354–364.
26. Freedberg DE, et al. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. Gastroenterology 2017;152:706–15.
27. Zhou B, et al. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 2016;27:339–47.
28. Maes ML, et al. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf 2017;8:273–97.
29. Cheungpasitporn W, et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail 2015;37:1237–41.
30. Lam JR, et al. Proton pump inhibitor and histamine-2 receptor antagonist use and iron deficiency. Gastroenterology 2017;152:821-829.e1.
31. Sun J, et al. The use of anti-ulcer agents and the risk of chronic kidney disease: a meta-analysis. Int Urol Nephrol 2018;50:1835–43.
32. Johnson DA, Fennerty MB. Heartburn severity underestimates erosive esophagitis severity in elderly patients with gastroesophageal reflux disease. Gastroenterology 2004;126:660–4.
33. Zirk-Sadowski et al. Proton-pump inhibitors and long-term risk of community-acquired pneumonia in older adults. J Am Geriatr Soc 2018;66:1332–8.
34. Jaynes M, et al. The risks of long-term use of proton pump inhibitors: a critical review. Ther Adv Drug Saf. 2019; 10: 2042098618809927.
35. BPAC NZ. Clinical Audit. Identifying patients who may benefit from "stepping down" PPI treatment. https://bpac.org.nz/audits/ppi.aspx
36. BPAC NZ. Stopping proton pump inhibitors in older people. 2019. https://bpac.org.nz/2019/ppi.aspx
37. Pharmaceutical Benefits Advisory Committee. March 2018 PBAC Outcomes - Other Matters. http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2018-03/other-matters-03-2018.pdf.
38. NPS MedicineWise. Proton pump inhibitors: PBS changes May 2019. https://www.nps.org.au/radar/articles/proton-pump-inhibitors-pbs-changes-may-2019#article
39. Waldum HL, et al. Rebound acid hypersecretion from a physiological, pathophysiological and clinical viewpoint. Scand J Gastroenterol 2010;45:389–94.
40. Evans N, et al. Dyspepsia and GORD care after PPI use. Br J Healthcare Management 2007;13:425–30.
41. Beardon P. Therapeutic strategies for managing gastroesophageal reflux in primary care. Scottish Primary Care 2007;Jan:16–7.
42. Kim J, et al. Strategies for Effective Discontinuation of Proton Pump Inhibitors. Curr Gastroenterol Rep. 2018;20:27.
43. American Gastroenterological Association. GERD Patient Study: Patients and Their Medications. Harris Interactive Inc; 2008.
44. El-Serag H, et al. Systematic review: persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies. Aliment Pharmacol Ther. 2010;32:720-37.
45. Fass R, et al. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease--where next? Aliment Pharmacol Ther. 2005;22:79-94.
46. Kaltenbach T, et al. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. Arch Intern Med 2006;166:965-71.
47. Sugimoto M, et al. Rabeprazole 10 mg q.d.s. decreases 24-h intragastric acidity significantly more than rabeprazole 20 mg b.d. or 40 mg o.m., overcoming CYP2C19 genotype. Aliment Pharmacol Ther 2012;36:627-34.
48. Basu K. Adult GORD: advances and challenges in management. March 2016. https://www.prescriber.co.uk/article/adult-gord-advances-and-challenges-in-management/
49. Kahrilas PJ. GERD pathogenesis, pathophysiology, and clinical manifestations. Cleve Clin J Med. 2003;70 Suppl 5:S4-19.
50. Boeckxstaens GE. Alterations confined to the gastro-oesophageal junction: the relationship between low LOSP, TLOSRs, hiatus hernia and acid pocket. Best Pract Res Clin Gastroenterol. 2010;24:821-9.
51. Kahrilas PJ, Boeckxstaens G. Failure of reflux inhibitors in clinical trials: bad drugs or wrong patients? Gut. 2012;61:1501-9.
52. Howden CW, Freston JW. Gastroenterology Today. 1996; 6:32–7.
53. Fletcher J, et al. Unbuffered highly acidic gastric juice exists at the gastroesophageal junction after a meal. Gastroenterology. 2001;121:775-83.
54. Kahrilas PJ. Management of the Acid Pocket. Gastroenterol Hepatol (N Y). 2014;10:587–89.
55. Kwiatek MA, et al. An alginate-antacid formulation (Gaviscon Double Action Liquid) can eliminate or displace the postprandial 'acid pocket' in symptomatic GERD patients. Aliment Pharmacol Ther 2011;34:59–66.
56. Rohof W, et al. Effect of PPIs on the size, position and acidity of the postprandial acid pocket. Gastroenterology 2012;142:S-92.
57. Leiman DA, et al. Alginate therapy is effective treatment for GERD symptoms: a systematic review and meta-analysis. Dis Esophagus. 2017;30(5):1–9.
58. Pouchain D, et al. Gaviscon® vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. A direct comparative randomised trial. BMC Gastroenterol. 2012;12:18.
59. Chiu CT, et al. Randomized clinical trial: sodium alginate oral suspension is non-inferior to omeprazole in the treatment of patients with non-erosive gastroesophageal disease. Aliment Pharmacol Ther 2013; 38: 1054-64.
60. Murie J, et al. Glad you brought it up: a patient-centred programme to reduce proton-pump inhibitor prescribing in general medical practice. Qual Prim Care 2012; 20: 141-8.
61. Coyle C, et al. Randomised clinical trial: addition of alginate-antacid (Gaviscon Double Action) to proton pump inhibitor therapy in patients with breakthrough symptoms. Aliment Pharmacol Ther 2017; 45: 1524-33.
62. Manabe N, et al. Efficacy of adding sodium alginate to omeprazole in patients with nonerosive reflux disease: a randomized clinical trial. Dis Esophagus. 2012;25(5):373–380.
63. Reimer C, et al. Randomised clinical trial: alginate (Gaviscon Advance) vs. placebo as add-on therapy in reflux patients with inadequate response to a once daily proton pump inhibitor. Aliment Pharmacol Ther. 2016;43(8):899–909.
64. Majithia R, et al. Are proton pump inhibitors safe during pregnancy and lactation? Evidence to date. Drugs 2012;72(2): 171–79.
65. Richter JE. Review article: the management of heartburn in pregnancy. Aliment Pharmacol Ther 2005;22(9):749–57.
66. Quartarone G. Gastroesophageal reflux in pregnancy: a systematic review on the benefit of raft forming agents. Minerva Ginecologica. 2013;65(5):541–9.
67. Tytgat GN, et al. Contemporary understanding and management of reflux and constipation in the general population and pregnancy: a consensus meeting. Aliment Pharmacol Ther 2003;18(3): 291–301.
68. Diav-Citrin O, et al. The safety of proton pump inhibitors in pregnancy: a multicentre prospective controlled study. Aliment Pharmacol Ther 2005;21(3): 269–75.
69. Gill SK, et al. The safety of proton pump inhibitors (PPIs) in pregnancy: a meta-analysis. Am J Gastroenterol 2009a;104(6): 1541–45.
70. Pasternak B, et al. Use of proton-pump inhibitors in early pregnancy and the risk of birth defects. N Engl J Med 2010;363(22): 2114–23.
71. Matok I, et al. The safety of fetal exposure to proton-pump inhibitors during pregnancy. Dig Dis Sci 2012;57(3): 699–705.
72. Gill SK, et al. The safety of histamine 2 (H2) blockers in pregnancy: a meta-analysis. Dig Dis Sci 2009b;54(9): 1835–38.
73. Dağlı Ü, Kalkan İH. Treatment of reflux disease during pregnancy and lactation. Turk J Gastroenterol. 2017;28(Suppl 1):S53-S56.
74. Sowa P, et al. Nonablative Radiofrequency Treatment for Gastroesophageal Reflux Disease (STRETTA). Gastrointest Endosc Clin N Am. 2020;30(2):253-65.

Reckitt Benckiser

This publication has been created with an educational grant from Reckitt Benckiser (New Zealand) Ltd. The content is entirely independent and based on published studies and the author's opinions. It may not reflect the views of Reckitt Benckiser.. Treatment decisions based on these data are the full responsibility of the prescribing physician.