

Alginates: From the ocean to gastroesophageal reflux disease treatment

Serhat Bor¹ , İsmail Hakkı Kalkan², Altay Çelebi³ , Dinç Dinçer⁴ , Filiz Akyüz⁵ , Peter Dettmar⁶ , Hasan Özen⁷ 

¹Division of Gastroenterology, Department of Internal Medicine, Ege University School of Medicine, Ege Reflux Study Group, İzmir, Turkey

²Department of Gastroenterology, TOBB University of Economics and Technology School of Medicine, Turkey

³Division of Gastroenterology, Kocaeli University School of Medicine, Kocaeli, Turkey

⁴Division of Gastroenterology, Department of Internal Medicine, Akdeniz University School of Medicine, Antalya, Turkey

⁵Division of Gastroenterology, Department of Internal Medicine İstanbul School of Medicine, İstanbul University, İstanbul, Turkey

⁶RD Biomed Limited, Castle Hill Hospital, Cottingham, UK

⁷Department of Pediatrics, Hacettepe University School of Medicine, Ankara, Turkey

Cite this article as: Bor S, Kalkan İH, Çelebi A, et al. Alginates: From the ocean to gastroesophageal reflux disease treatment. *Turk J Gastroenterol* 2019; 30(Suppl 2): S109-36.

Alginates: From the ocean to gastroesophageal reflux disease treatment

The management of gastroesophageal reflux (GERD) disease is based on proton-pump inhibitor (PPI) therapy. However, alginates are an alternative therapeutic approach, either as a monotherapy or in combination with PPIs that play an important role in treatment. In this article, we evaluated the following topics in relation to alginates:

1. Definition and epidemiology of GERD
2. Production and mode of action of alginates
3. Efficacy of alginate monotherapy for the treatment of mild GERD symptoms
4. The role of alginates in combination with PPIs in patients with severe or PPI-unresponsive GERD
5. The efficacy of alginates in regurgitation-dominant GERD
6. Alginates in the management of atypical GERD symptoms
7. Long-term and/or on-demand use
8. The role of alginates in the step-down or cessation of PPI therapy
9. Alginates in the treatment of GERD in children
10. Alginates in pregnancy and lactation
11. Safety

Definition and epidemiology of gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is defined as a "condition which develops when the reflux of gastric content causes troublesome symptoms or complications" (1).

However, there is no accepted universal definition of the symptoms of GERD and its complications. Additionally, there are significant differences among various racial groups in terms of the understanding and the experience of the symptoms of GERD. For example, there is no word for heartburn in Dutch, Malay, Mandarin, Chinese, or Korean. In an interracial study by Spechler et al. (2) most of the participants (65.9%) did not understand the meaning of the term heartburn, while 22.8% of patients who denied having heartburn in fact experienced symptoms that physicians might consider to be heartburn.

Recently, an international study group defined pathological GERD as the presence of at least one of the following criteria: grade C or D esophagitis in upper gastrointestinal (GI) endoscopy, esophageal peptic stricture, Barrett's mucosa longer than 1 cm and esophageal acid exposure >6% in 24-hour impedance-pH-metry (3). According to this definition, there are a tremendous number of patients stay in the gray zone.

Epidemiology of GERD and its complications

GERD has a global impact on health and impairs the health-related quality of life of a substantial proportion of the global population. A recent meta-analysis showed that there was a statistically significant increase in the prevalence of GERD worldwide in the last 20 years (4). The pooled prevalence of GERD symptoms that occurred at least weakly reported from population-based studies worldwide is approximately 13%, but there is considerable geographic variation. Because there is heterogeneity in study designs, it is difficult to accurately estimate the

Corresponding Author: İsmail Hakkı Kalkan; drismailster@gmail.com

Received: August 23, 2019 Accepted: August 28, 2019

© Copyright 2019 by The Turkish Society of Gastroenterology · Available online at www.turkjgastroenterol.org

DOI: 10.5152/tjg.2019.19677

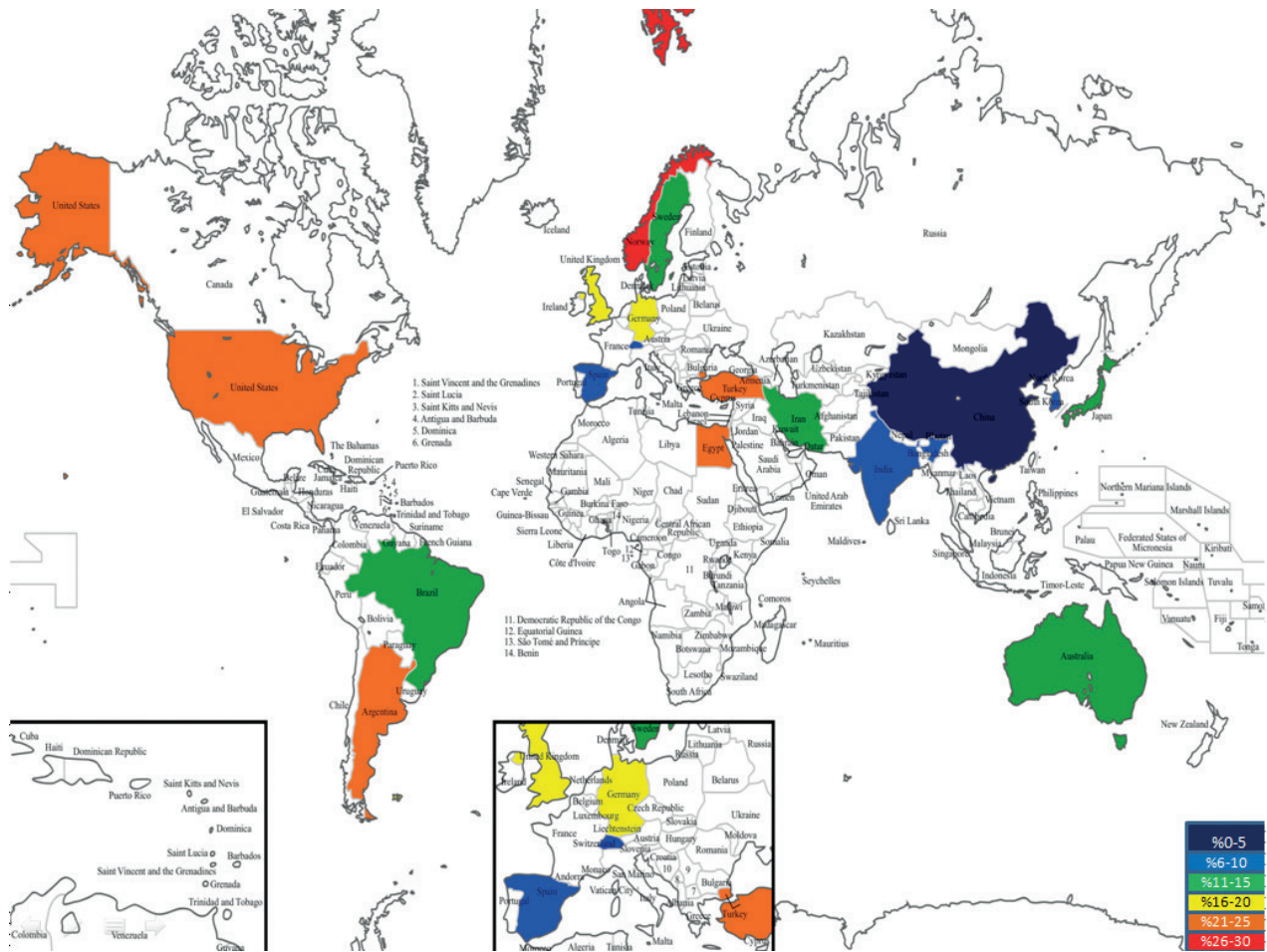


Figure 1. Distribution of GERD prevalence worldwide (12).

prevalence of GERD. However, most studies have revealed that the prevalence of GERD appears to be highest in South Asia and Southeast Europe (> 25%) and lowest in Southeast Asia, Canada, and France (<10%) (5) (Figure 1).

In Turkish GERD epidemiological studies, the prevalence of GERD was found to be 20% (6), 19.3% (7), 12.5% (8), and 22.8% (9,10) when evaluated with the Mayo questionnaire. The GERD Questionnaire (GERD-Q) was used in one study, and the prevalence was found to be 24.7% (11). According to these 5 studies, the pooled prevalence of GERD in Turkey was calculated to be 23%. Regurgitation was more common than heartburn in all of the studies. In the cumulative evaluation, the prevalence rates were 23% for regurgitation and 19% for heartburn (12). These data confirm that the prevalence rate of GERD in Turkey is similar to that in European countries, while

regurgitation as the predominant symptom is similar to studies from Asian countries.

Erosive esophagitis (EE) is one of the most common complications of GERD. The prevalence difference of EE in Western countries is larger than Eastern countries in symptomatic patients. In 3 population-based studies, the prevalence of EE in symptomatic GERD ranged from 6.4-15.5%, while the prevalence of EE in asymptomatic patients ranged from 6.1-9.5% (13-15). Although EE is more common in Western countries, the distribution of EE severity seems to be similar in both geographic areas (14,16). Only a small proportion of patients with EE have severe esophagitis findings in endoscopy (13-16). In Turkey, the prevalence of EE in symptomatic GERD patients seems to be similar to that observed in Western countries. Additionally, the distribution of EE severity is not different from that in the rest of the world (17).

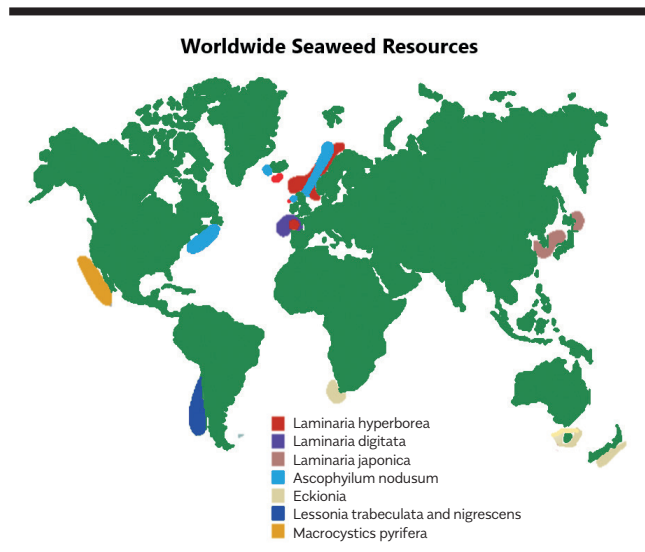


Figure 2. The world distribution of the various seaweeds that have been commercialized.

As seen in GERD, the prevalence of Barrett's esophagus (BE) is higher in Western countries (18) than in Eastern countries. Gerson et al. (19) found that short-segment BE with histologically confirmed intestinal metaplasia was found in 17% of asymptomatic patients who underwent colonoscopy screening. In another study, the prevalence of BE was 65 out of 961 (6.8%) patients, which included 12 (1.2%) patients with long-segment BE (20). In contrast to the abovementioned data, the findings of a recent meta-analysis showed that the pooled prevalence of histologic BE in Asian countries was similar to that in Western countries (1.3% vs 1.6%). Additionally, the prevalence of low-grade dysplasia, high-grade dysplasia, and esophageal adenocarcinoma (EAC) in histologic BE in Eastern countries was similar to that in Western countries (21). The prevalence of histopathologically confirmed BE in Turkish cohorts (0.6%) was much lower than that in Eastern and Western cohorts (9,17,22,23). In a study comparing immigrants and Dutch inhabitants in the Netherlands, reflux disease was less prevalent in immigrants, who were mostly of Turkish descent, than among native Dutch individuals. Additionally, there were no patients with BE among the Turkish immigrants (24).

The prevalence of EAC varies geographically, and several studies have documented that the incidence of EAC has tended to increase in the last 20 years in Northern and Western Europe, Northern America, and Oceania. The highest incidence of EAC was observed in the United Kingdom (7.2/100,000 person-years in men and

2.5/100,000 person-years in women), the Netherlands, Ireland and the United States, in that order. The lowest incidence rates were observed in sub-Saharan Africa (25). GERD is a common disorder, but there are some differences according to the geographical areas. These differences might have an impact on the selection of medications, similar to regurgitation-dominant disease.

Production and mode of action of alginates

Alginate-based pharmaceutical formulations have been successfully used to treat the symptoms of GERD for decades and have a rapid onset of symptom relief. In the last twenty years, the knowledge and awareness of GERD has grown from the classical reflux symptoms of heartburn and regurgitation to the symptoms of extraesophageal reflux (EER), also known as airway reflux, silent reflux and laryngopharyngeal reflux disease (LPR). This increased awareness has led to a far greater understanding of the reflux of gastric contents in the airways, lungs, and ears, leading to a myriad of additional ear, nose, and throat (ENT) and respiratory symptoms, which we now know may be indications for the use of alginate-based pharmaceutical products. Research and clinical studies have demonstrated that upwards of 40% to 60% of Western populations can benefit from alginate-based products, and this benefit is quickly growing in other regions of the world where reflux disease is now recognized as a real and growing problem.

Alginates naturally occur as structural polysaccharides in brown algae (seaweed). The nature of alginates as well as the production and mode of action are summarized below.

1. The harvesting of alginates

There are many different alginates with different chemical structures and properties, and the function of the alginate determines the application and the end product for which it is used. Today, alginate production is mainly based on harvested *Macrocystis pyrifera* in the USA, *Durvillaea* spp. and *Lessonia* spp. in Chile and small amounts of *Ecklonia* spp., *Eisenia* spp. and *Laminaria japonica* in the Far East. In Europe, the raw materials include *Laminaria digitata* in France and *Ascophyllum nodosum* and *Laminaria hyperborea* in Norway. The worldwide distribution of the various seaweeds that have been commercialized is illustrated in Figure 2.

The diversity of the seaweed harvest sites is reflected in the differences in the characteristics and properties of the various alginates. The most important seaweed in

terms of pharmaceutical products is *Laminaria hyperborea*. The mechanization of the harvest of this particular seaweed species began in 1964, and the method of harvesting has developed along the west coast of Norway, in an area from the south to the Lofoten Islands in the north of the country (Figure 2, 3).

2. Chemical composition and physical properties of alginate

The chemical composition of alginates is variable to a certain extent. The composition varies according to the seaweed species and even within the different parts of the same plant. The composition is also affected by seasonal changes and by the roughness of the sea.

Alginate occurs both in brown algae and in certain bacteria and can be considered both a phycocolloid and a microbial polysaccharide. Alginates belong to a family of linear copolymers containing 1,4-linked β -D-mannuronic acid (M) and 5-epimer α -L-guluronic acid (G). The distribution of M and G in alginate chains gives rise to three different block types, namely, poly-M blocks, poly-G

blocks and alternating M-G-M-G blocks i.e., MG blocks. Alginates isolated from different algae can vary both in the monomer composition and the block arrangement, and these variations are also reflected in the properties of the alginate.

Alginate forms strong gels with divalent cations, such as Ca^{2+} , giving both strength and flexibility to the algal tissue. While the viscosity depends mainly on the molecular size, the affinity for cations and the gel-forming properties of the alginate are mostly related to the guluronic monomer content. When two guluronic acid monomer residues are adjacent in the polymer, they form a binding site for polyvalent cations. The content of the G-blocks is therefore the main structural feature contributing to the gel strength and stability, thus making the stem of *Laminaria hyperborea* ideal for use as a raft-forming agent to suppress gastric reflux.

Further information regarding the detailed chemical composition of alginates can be obtained by nuclear magnetic resonance (NMR) spectroscopy. By high-resolution NMR, it is possible to determine the complete M-G profile of an alginate, including information on the three neighboring units and the average block lengths. Table-1 shows the typical M and G profiles for alginates from different seaweeds, clearly indicating that the alginate characterization varies between seaweed species.

3. Alginates are different

Alginates produced from different seaweeds have different chemical compositions and physical properties. Only certain alginates have the right characteristics to be used to manufacture effective reflux-suppressant products. The mode of action of these products is physical rather than pharmacological.



Figure 3. Harvesting mechanization of *Laminaria hyperborea*

Table 1. Typical M and G profiles for alginates from different seaweed species.

Raw material	F _G	F _M	F _{GG}	F _{MG+GM}	F _{MM}	F _{GGG}	F _{MGM}	F _{GGM}	N _{G>1}	Gel strength
<i>Laminaria hyperborea</i> (stem)	0.70	0.30	0.57	0.26	0.17	0.52	0.04	0.04	17	High
<i>Laminaria hyperborea</i> (leaf)	0.55	0.45	0.26	0.38	0.36	0.29	0.12	0.05	9	Medium
<i>Macrocystis pyrifera</i>	0.39	0.61	0.16	0.46	0.38	0.12	0.20	0.03	6	Medium - low
<i>Ascophyllum nodosum</i>	0.36	0.64	0.16	0.40	0.44	0.12	0.15	0.15	4	Medium - low
<i>Lessonia nigrescens</i>	0.40	0.60	0.22	0.38	0.40	0.20	0.14	0.04	7	Medium - low
<i>Lessonia trabeculata</i>	0.67	0.33	0.55	0.23	0.22	0.50	0.07	0.05	12	High - medium
<i>Laminaria japonica</i>	0.34	0.66	0.16	0.36	0.48	0.13	0.15	0.03	6	Medium - low
<i>Laminaria digitata</i>	0.41	0.59	0.25	0.32	0.43	0.20	0.11	0.05	6	Medium - low
<i>Durvillea antarctica</i>	0.31	0.69	0.18	0.27	0.56	0.14	0.09	0.04	6	Low

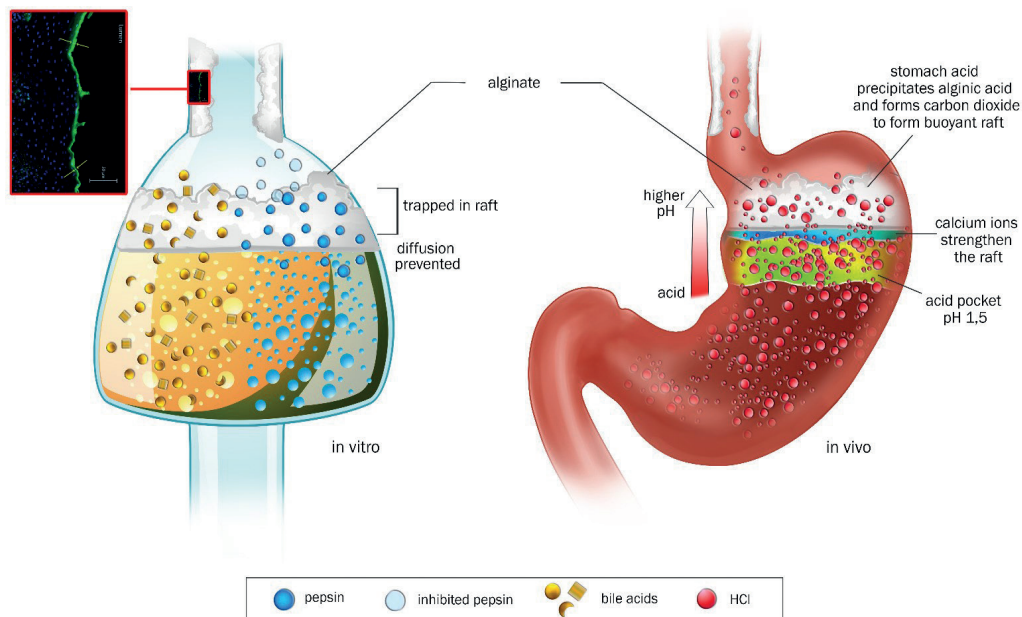


Figure 4. Mode of action of sodium alginate

Table 2. The rafting performance of product batches prepared with Na alginates from different seaweeds.

Alginate source (seaweed species)	Raft description	Raft volume	Raft buoyancy	Raft strength	Raft shrinkage
<i>Ascophyllum nodosum</i>	No raft formed	-	-	-	-
<i>Durvillea antarctica</i> 80% <i>Lessonia nigrescens</i> 20%	Weak, inconsistent	38 mL	Floats below liquid surface	4 g	high
<i>Lessonia nigrescens</i>	Weak, uniform	55 mL	Floats below liquid surface	7 g	medium
<i>Laminaria hyperborea</i> (stem)	Strong, coherent uniform	60 mL	Floats below liquid surface	12 g	minimal

The three active ingredients of the most effective products are sodium (Na) alginate (*Laminaria hyperborea* stem), Na bicarbonate (HCO₃) and calcium (Ca) carbonate (CO₃). These substances interact to form a strong, coherent, voluminous, buoyant alginate raft when they are introduced to the acidic gastric environment. The raft is responsible for suppressing reflux and relieving the symptoms of heartburn and GERD.

The experience of alginate product manufacturing has shown that the type of alginate used is very important for the formation of buoyant, voluminous, strong and coherent rafts. Only alginates with a very low molecular weight and high gel strength are suitable for the manufacture of effective reflux-suppressant products. Alginates from different species of seaweed and different parts of the

same seaweed, for example, the leaf, have different molecular compositions, and these differences in composition can determine whether or not the product forms a coherent, buoyant raft or whether it forms a raft at all.

Table 2 shows the rafting performance of products prepared with low-molecular weight Na alginates conforming to the European Pharmacopeia monograph that were derived from different seaweed sources. The rafts were formed by adding a 20-mL dose of product to 150 mL of 0.1 M HCl and incubating the mixture at 37°C for a period of 30 minutes. Table 2 shows that only the product made with Na alginate extracted from the stems of *Laminaria hyperborea* was able to form strong, coherent, voluminous and highly buoyant rafts. This product also had a larger raft thickness and acid neutralization capacity (26). Products

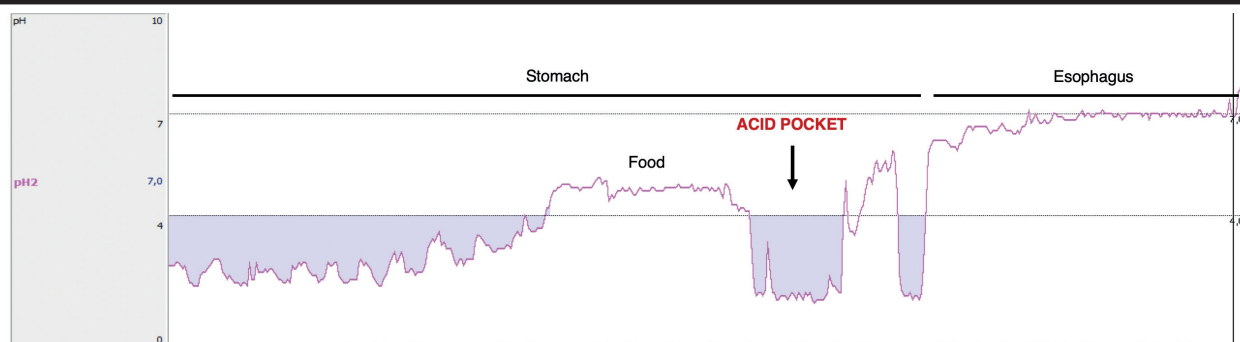


Figure 5. Acid pocket, as measured with a pH catheter, in the proximal stomach following food intake (Ege University School of Medicine, Motility Lab).

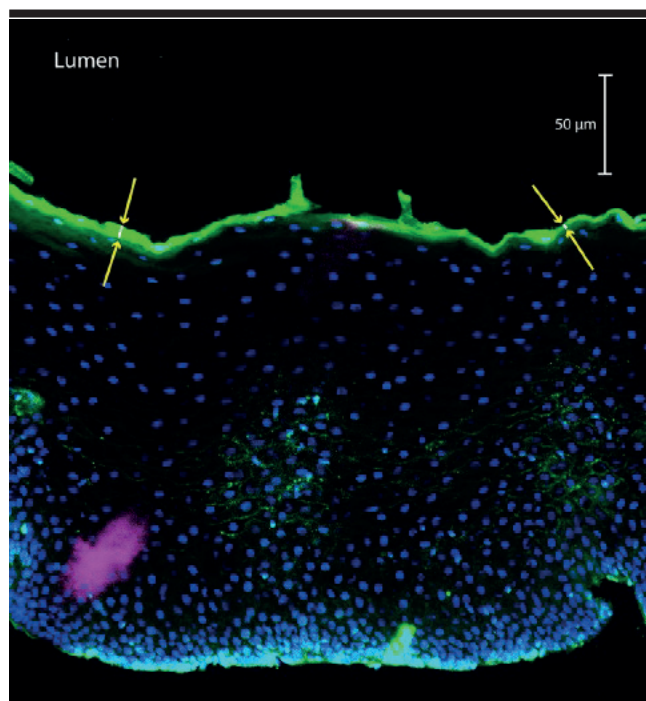


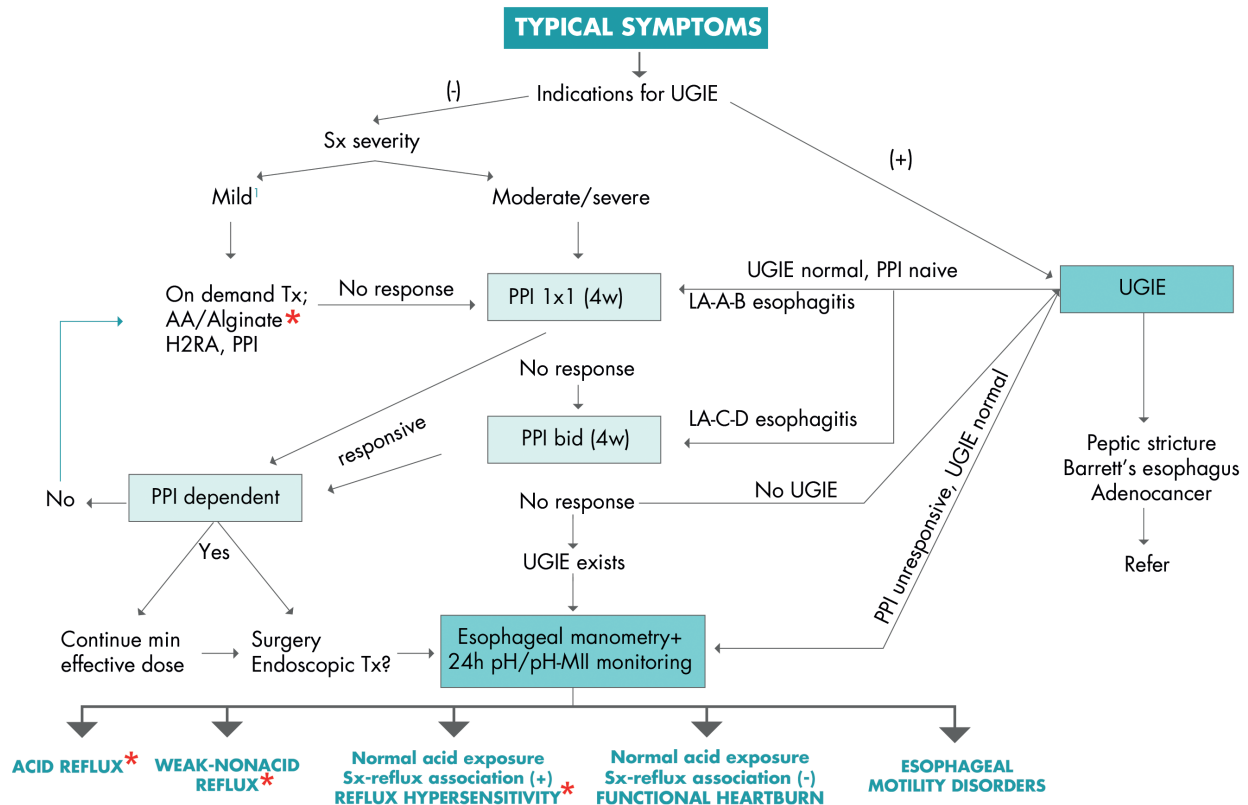
Figure 6. Microscopy at 20x under an epifluorescence microscope, showing fluorescein-labeled alginate on the luminal surface of the biopsy mucosa after 1 hour of washing in a neutral solution. Nuclei are stained with DAPI. Yellow arrows indicate example thickness measurements.

made with alginate extracted from the other sources in the table either formed weaker, inconsistent rafts with lower volumes and poor buoyancy or did not form rafts at all.

4. Mode of action

Alginates have a unique, nonsystemic, physical, rather than pharmacological, mode of action, and the selection of the correct alginate is essential for the performance in several key areas, as listed below.

1. Prevention of gastric reflux.
 - a) Suppression of gastric reflux. The G-block structure of an alginate contributes to the gel strength, which results in a reaction between Na alginate and the acid present in the stomach, producing a low-density viscous gel that floats on top of the stomach. This forms a physical barrier that protects the delicate esophageal mucosa and the airways from the gastric refluxate (26,27).
 - b) Prevention of postprandial reflux. The physical barrier formed by alginate is also very important for eliminating or displacing the acid pocket that has been identified in GERD patients (Figure 5). The acid pocket forms at the gastroesophageal junction after a meal and consists of an unbuffered, highly acidic gastric juice and has pathological relevance in GERD. A strong alginate raft can cap the acid pocket and reduce or even prevent postprandial acid reflux (28,29).
2. Inhibition of pepsin and bile acids. Alginate can remove both pepsin and bile acids from gastric refluxate, limiting their diffusion and specifically affecting the enzymatic activity of pepsin (30).
3. Topical protection. Alginates play a major role in the topical protection of the vulnerable and sensitive esophageal mucosa, reducing the risk of inflammation as a result of the components of the gastric refluxate, such as acid, pepsin and bile acids. Suspensions of the correct Na alginate can form adherent viscous layers on contact with the esophageal mucosa and demonstrate bioadhesive potential in this area, which is highly susceptible to potential damage from the components of gastric reflux (31,32). In a recent study by Woodland et al. (31), 3D-cell culture was used to analyze the protective effect of a topically applied alginate solution. The apical surface



***Potential Indications for Alginate**

¹Mild Sx; <3/w, short-term, Minimally effective for daily activities

Figure 7. Algorithm for patients with typical reflux symptoms and indications for alginate in the treatment of GERD (adapted from 40).

UGIE: Upper-GI endoscopic indications; Sx: symptom; AA: antacids.

Indications for UGIE: >50 years old, Sx duration >5 years, dysphagia, odynophagia, GI system (GIS) bleeding, weight loss, recurrent vomiting, unexplained anemia, first-degree relatives with upper-GI cancer.

was covered and protected by alginate or a control solution. Similar to these models, human esophageal biopsies were placed into Ussing chambers and were then coated. A pH 3 bile acid solution was applied, and transepithelial resistance (TER) values were measured in both models. The luminal sides of all tissues were covered with adherent alginate. The decrease in TER in alginate-coated tissues was significantly lower than that in the controls. This finding implies that the application of alginates augments tissue resistance in vitro (Figure 6).

Efficacy of alginate monotherapy for the treatment of mild GERD symptoms

Heartburn and regurgitation are typical symptoms of GERD and reduce the quality of life for millions of people.

Approximately 50-80% of patients have symptomatic (endoscopy-negative or nonerosive) or mild erosive GERD (grade I, Savary/Miller or Los Angeles (LA)-A, B) (12,33). Acid suppression is the mainstay of therapy for GERD, and proton-pump inhibitors (PPIs) are the most potent acid-suppressing drugs. However, in some patients, especially those with nonerosive reflux disease (NERD), acid-suppressive therapy with PPIs is not as successful.

Alginates are medications that work through an alternative mechanism, by displacing the postprandial gastric acid pocket. The acid pocket is a short zone of unbuffered highly acidic gastric juice that occurs below the esophagogastric junction after meals. Conventional mechanisms, such as transient lower esophageal sphincter relaxation (TLESR) and hiatal hernias, may increase GERD

Table 3. Alginate monotherapy vs other therapies for GERD treatment.

Study	Comparator	Odds ratio (OR) (95% confidence interval (CI))
Beeley et al. (1972)	Placebo	4.89 (1.83-13.07)
Chevrel et al. (1980)	Antacid	17.97 (6.15-52.51)
Lai et al. (2006)	Antacid	3.86 (1.81-8.22)
Goves (1998)	PPIs	0.24 (0.15-0.37)
Pouchain et al. (2012)	PPIs	0.68 (0.41-1.13)
Chiu et al. (2013)	PPIs	1.11 (0.62-1.99)

PPIs: Proton-pump inhibitors.

by enhancing the acid pocket (29,34). In the presence of gastric acid, alginate forms a foamy gel that is similar to a raft floating on the surface of the gastric contents, and this barrier-like gel prevents acid reflux in GERD. In vitro and in vivo studies have demonstrated an immediate onset of therapeutic effects with alginate (within 1 hour of administration) that is faster than that of a PPI or an H2 receptor antagonist (H2RA) (35). Compared with antacids, alginate-based formulations are more effective in controlling postprandial esophageal acid exposure and in relieving reflux symptoms, including heartburn, regurgitation, vomiting and belching, with a longer duration (36-38). Alginate-based formulations are also noninferior to omeprazole in achieving a heartburn-free period in patients with moderate episodic heartburn (39). Additionally, the Turkish reflux study group consensus report recommended alginate monotherapy as an initial therapy for patients with mild GERD (40) (Figure 7).

Alginate monotherapy has been shown to be superior to placebos and antacids for decreasing GERD symptoms in patients with NERD in several studies (41,42). In a recent meta-analysis (33), alginate was shown to be superior to the placebo in one study, while it was more effective than antacids in two other studies. Additionally, the effect of alginate was comparable to that of omeprazole in three different studies (39,43,44) (Table 3).

In a study by Giannini et al. (45), symptom resolution was higher and the speed of action was faster in the alginate group than that in the antacid group. In another more recent study, the level of complete symptom relief was similar in patients receiving omeprazole or alginate (60% vs. 56.7 for intention-to-treat (ITT), $p=0.7$, respectively and 66.7% vs 65.4% for per protocol, $p=0.7$, respectively). In an open-label placebo-controlled study, alginate significantly decreased heartburn frequency compared

with placebo (46). A double-blind randomized controlled trial showed that Gaviscon, an alginate-antacid formulation, achieved more relief of reflux symptoms, including heartburn and regurgitation, in patients with both NERD and EE (47).

In conclusion, alginate is superior to placebos and antacids for the treatment of mild GERD, and alginate monotherapy seems to be beneficial as an initial treatment for mild GERD. There are limited data comparing alginate and PPIs for the treatment of mild GERD. The only agent tested in a limited number of studies was omeprazole, and the effect of omeprazole was comparable to that of alginate for decreasing typical GERD symptoms. Further studies with next-generation PPIs are required to confirm these data.

The role of alginates combined with PPIs in patients with severe or PPI-unresponsive gastroesophageal reflux disease

There are different definitions of severe symptomatic GERD in the literature. According to the Turkish Reflux Study Group Consensus Report, moderate/severe symptomatic reflux was defined as 3 or more heartburn or regurgitation in a week, affecting daily activities (40). Endoscopic severe esophagitis is defined as LA grade C or D esophagitis (48). Although several studies have analyzed the efficacy of adding alginic acid to PPIs, most of these studies included patients who did not adequately respond to PPIs or who had symptomatic breakthroughs (49-51). For instance, in a multicenter study, improvements in the Heartburn Reflux Dyspepsia Questionnaire (HRDQ) reflux score and the number of night-time symptoms in patients who remained symptomatic despite single-dose PPIs were significantly higher in the PPI+Gaviscon Advance group than those in the PPI+placebo group. The authors of this study concluded that adding alginate to the treatment plan can decrease the burden of reflux symptoms in PPI-unresponsive patients (50). One of the major limitations in these studies was the lack of the symptomatic or endoscopic stratification of patients as having mild or moderate/severe disease before randomization and that all of the patient data was pooled together (49-51).

Sodium alginate combined with omeprazole has been shown to be better than omeprazole alone in terms of complete symptom resolution at the end of the study (56.7% vs 25.7%, $p<0.05$) in Japanese patients with NERD. In that study, the symptom frequency was at least 2 days per week during the 1-month period before entering the study (49) (Figure 8).

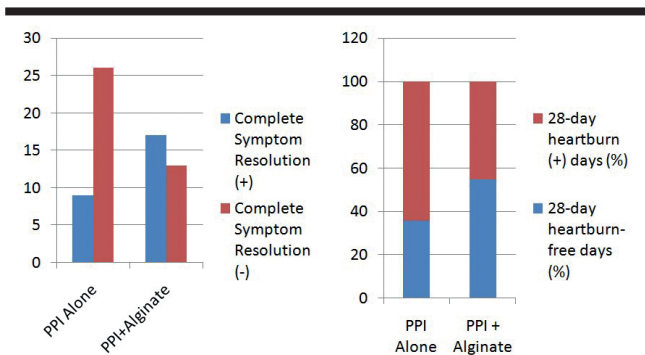


Figure 8. The rate of the complete resolution of heartburn for 7 consecutive days and heartburn-free days (%) during the 28-day observation period was significantly higher in the PPI+alginate combination group than in the PPI alone group (49).

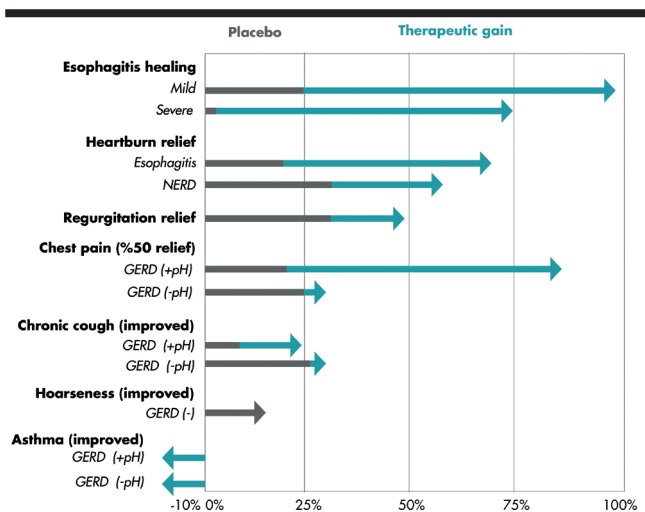


Figure 9. Summary of PPI efficacy for the potential manifestations of GERD, as assessed in randomized controlled trials (57).

PPI therapy is a first-line approach to ensure endoscopic healing and symptom control in patients with GERD. However, a substantial subgroup of patients with well-defined GERD will continue to experience reflux symptoms despite adequately dosed PPI therapy (52,53). While there is no universal definition for PPI “failure,” the presence of heartburn and/or regurgitation and an impaired quality of life despite adequate doses of PPIs may be indicative of PPI failure. The Turkish reflux study group defined PPI unresponsiveness as “in patients without alarm symptoms, if there is less than 50% recovery in typical reflux symptoms after 4 weeks qd PPI treatment following nonresponsive 4-week bid PPI treatment” (40).

These patients are considered to have refractory GERD (rGERD). Several studies have shown that adding alginate to existing PPI therapy aids in the control of GERD symptoms (49-51). In a multicenter study of 134 patients with GERD symptoms, adding an alginate-antacid suspension to once-daily PPI treatment decreased the severity and frequency of heartburn, the frequency of regurgitation and the number of days with night-time symptoms.

Although PPIs have become the main therapy for severe symptomatic GERD or severe EE, it has been well documented that the durability of this therapeutic effect is less notable. In a recent systematic literature review, it was reported that breakthrough symptoms after PPI treatment were found in 30-60% (54). The effect of alginic acid as an add-on treatment was compared with the effect of a placebo in GERD patients with an insufficient control of heartburn and/or regurgitation despite a once-daily PPI in two parallel study arms (exploratory study arm and confirmatory study arm). Symptomatic improvement was observed with an add-on alginic acid-antacid combination, but there was no significant difference in the response to this treatment vs that to the placebo in the confirmatory arm (51-48%, respectively) (OR (95% CI): 1.15 (0.69-1.91), p=0.594), while there was a significant difference in the exploratory arm (75-36%, p<0.05) (51).

Rinaldo et al. (55) showed that adding alginate to the treatment improved GERD symptoms in patients who were refractory to 8 weeks of PPI treatment and had weak acid reflux that was documented with multichannel intraluminal impedance pH (MII-pH) monitoring.

The overall results from these studies provide evidence that add-on alginate helps reduce reflux symptoms in patients with an insufficient response to PPIs. This effect is particularly high in patients with weak acid/non-acid reflux.

The efficacy of alginates in regurgitation-dominant gastroesophageal reflux disease

The typical symptoms of GERD include heartburn and regurgitation. Regurgitation is defined as the perception of the flow of refluxed gastric content into the mouth or hypopharynx (1). Although PPIs have satisfactory therapeutic effects for heartburn, the relative therapeutic gain for regurgitation obtained by PPIs is evidently lower than the therapeutic gain for heartburn. In a systematic literature review performed by Kahrilas et al. (56), seven placebo-controlled trials were analyzed, and the rel-

Table 4. The results of studies on the efficacy of alginates in the reduction of regurgitation.

Study	Study Protocol	Control group	ITT patients (n)	Relief of regurgitation	p
Thomas E, 2014 ⁽⁵⁹⁾	Pilot, randomized, double-blind, placebo-controlled	Placebo	110	Alginate was better	0.0137
Wilkinson J, 2019 ⁽⁶⁰⁾	Multicenter, randomized, double-blind, placebo-controlled	Placebo	424	Alginate was better	0.029
Lai IR, et al 2006 ⁽³⁸⁾	Prospective, randomized, and active controlled	Antacid	121	Alginate was better	0.0006
Chiu CT, et al 2013 ⁽⁴⁴⁾	Randomized	Omeprazole	183	Same**	0.487

ITT: Intention-to-treat (ITT); ** Relief of heartburn or regurgitation.

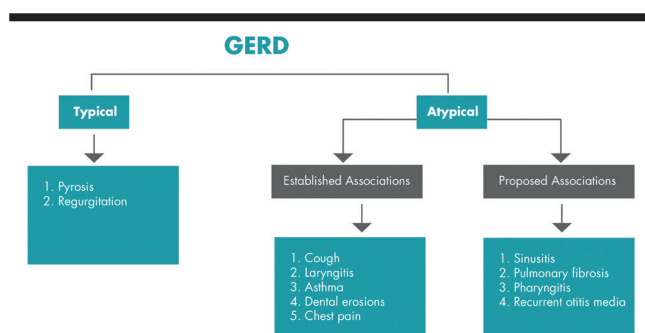


Figure 10. Classification of GERD (Turkish Reflux Study Group Consensus Report, 61).

ative therapeutic gain obtained with PPIs was only 17% for regurgitation, while it was >20% for heartburn. The therapeutic effects of PPIs are summarized in Figure 9, including a comparison of the efficacy of PPIs in treating esophagitis with their efficacy in treating other GERD syndromes (57) (Figure 9).

In a 24-hour intraesophageal impedance-pH monitoring study, Zerbib et al. (58) showed that there were more reflux events associated with regurgitation than with heartburn in PPI-refractory patients. These data support the idea that persistent regurgitation is a major cause of a lack of a complete response to PPI treatment. Alginic acid, a rafting anti-reflux agent, forms a foamy gel that floats on the surface of gastric contents when it interacts with gastric acid (32). Since it generates a barrier-like gel that sits above the gastric contents, alginate theoretically has specific properties that can prevent regurgitation.

In support of these data, a randomized, double-blind, placebo-controlled clinical trial showed that there was a greater decrease in regurgitation symptoms in the al-

ginic and antacid combination group than in the placebo group (least-squares mean difference -0.62; $p=0.0033$) (59). Additionally, a multicenter study showed that an alginic acid and antacid combination was more efficient in decreasing regurgitation events in GERD patients than a placebo (least-squares mean difference -0.28; $p=0.029$) (60). Lai et al. (38) showed that an alginic acid and antacid combination was more efficient for decreasing regurgitation events in patients with NERD at the end of the 6 weeks of treatment than antacid monotherapy ($p=0.008$). Chiu et al. (44) reported that the effect of alginic acid was comparable to that of omeprazole for decreasing regurgitation or heartburn frequency in patients with GERD. This study had some limitations. For example, patients who were diagnosed with NERD and heartburn or regurgitation (either one) as the main symptom (at least 2 days a week) were enrolled in this study. For these reasons, this study included patients with only heartburn and patients who experienced symptoms more than 2 days a week (patients with severe GERD) (44) (Table 4).

In conclusion, PPIs are the mainstay of medical management for GERD. Although PPIs provide relief from most symptoms, reflux may persist and alginates relieve regurgitation more effectively than placebo and antacids.

The role of alginates in the management of atypical gastroesophageal reflux disease symptoms

According to the Turkish Reflux Study Group Consensus Report, the established GERD-associated conditions include cough, laryngitis, asthma, dental erosion and chest pain (61) (Figure 10). GERD typically presents with esophageal symptoms such as heartburn and regurgitation (62); however, it may also present with extraneous symptoms (63).

Laryngopharyngeal reflux disease (LPR) is an extraesophageal variant of GERD that refers to the retrograde flow of gastric contents to the larynx and pharynx. Extra-esophageal reflux symptoms in LPR may develop in two ways. Injury may occur via the exposure to the gastric acid, pepsin and bile salts in the laryngopharyngeal area in the "direct injury" or "reflux" theory. The other theory is the "reflex" theory. According to this theory, mucosal receptors are stimulated by reflux material, which then activate inflammatory mediators that cause extraesophageal symptoms such as a bronchial cough reflex or globus sensation (63).

In the Progression of Gastrointestinal Reflux Disease (ProGERD) study, Jaspersen et al. (64) reported that the extraesophageal symptom rate was 32.8%. The most common extraesophageal symptom was chest pain (14.5%), followed by chronic cough (13%). The extraesophageal symptom rate was significantly higher in EE (34.9%) than in nonerosive esophagitis (30.5%).

Non-cardiac chest pain

PPIs are the therapy of choice for patients with non-cardiac chest pain (NCCP) due to their high potency and effective acid inhibition. Reflux-related NCCP shows the highest response rate of the entire GERD spectrum (number-needed-to-treat (NNT)=1.7) (65). In a randomized, double-blind, placebo-controlled trial, the overall treatment response to omeprazole 20 mg twice daily for 8 weeks was 81% and was superior to that of placebo in patients with GERD-related NCCP, as documented by 24-hour esophageal pH testing (66). In a recent meta-analysis, Leiman et al. (33) showed that alginate was also capable of improving global GERD symptoms, including NCCP.

Cough

Cough is another extraesophageal symptom of GERD, and GERD is one of the three most common causes of chronic cough. In uncontrolled studies, PPIs were shown to improve symptoms; however, in a double-blind randomized study, only 35% of patients responded to omeprazole (40 mg/day) treatment (67). Additionally, a meta-analysis of placebo-controlled studies documented the ineffectiveness of PPI therapy for chronic cough (68). It should be noted that the uncertainty of the association between chronic cough and GERD in these studies is most likely due to inappropriate patient selection because of the uncertainty of the diagnostic tests.

Adding alginic acid to PPI treatment has been shown to be effective for the resolution of chronic cough related to

GERD. In a study by Lieder et al. (69) 15 patients received lansoprazole 15 mg twice daily and a 10-mL standard dose of Gaviscon Advance (Reckitt Benckiser, Kingston-upon-Thames, UK) (containing Na alginate 1 g/10 mL and potassium (K) HCO₃ 200 mg/10 mL) at bedtime for at least 2 months. Chronic cough was resolved in 93% (14/15) of patients (69).

Laryngopharyngeal reflux

The pathophysiology of LPR is suggested to be a result of two main mechanisms that are similar to those in cough. The first of these mechanisms is vagally mediated throat clearing and coughing responses causing physical laryngeal injury that results from the irritation of the distal esophagus by refluxed gastric contents. The other mechanism of laryngeal injury is direct contact with erosive gastric refluxate. Although PPIs are able to remove acidic components of the gastric refluxate, they are unable to neutralize other more damaging gastric components, such as pepsin and bile acids (70).

PPIs are the standard therapy for patients with suspected LPR. In open-label studies, PPIs have been shown to be beneficial for decreasing LPR symptoms (71,72). However, there is growing evidence from randomized placebo-controlled trials that PPI treatment is not effective for the treatment of LPR. For instance, in contrast to these open-label uncontrolled studies, a placebo-controlled multicenter study showed that esomeprazole 40 mg (twice a day) was comparable to placebo in regard to the symptomatic response in suspected LPR patients (73). Similarly, in a more recent meta-analysis of controlled studies, PPI therapy was found to be ineffective for LPR (74).

Alginate, sometimes in combination with PPIs, has been indicated to be effective in the treatment of the symptoms of reflux as well as in the treatment for EER symptoms. Alginate produces a mechanical antireflux barrier above the gastric acid pocket. This barrier reduces the risk of further symptoms by preventing the reflux of gastric contents, including pepsin and bile salts, into the esophagus and aerodigestive area (75). In a study by McGlashan et al. (76) LPR patients who received a liquid alginate suspension had significant improvements in symptom scores and clinical findings compared to patients who received the control. In another study conducted by Tseng WH et al. (77), liquid alginate significantly improved symptoms (decrease in the reflux symptom index (RSI) scores) and the number of reflux episodes with 24-hour intraesophageal MII-pH monitoring when compared

with baseline, but was not superior to placebo. Wilkie MD et al. (78) reported that alginate alone was comparable with alginate+PPI combination for decreasing RSI scores ($p=0.75$) in patients with LPR. The authors concluded that alginic acid monotherapy was capable of treating LPR and was a safe and low-cost empirical treatment.

In conclusion, PPI treatment is the standard of care for the diagnosis and therapy of patients suspected of having extraesophageal GERD symptoms. However, the therapeutic effect of PPIs for extraesophageal symptoms is not satisfactory compared to that of typical GERD, and the treatment of the extraesophageal manifestations of GERD remains a challenge. According to these findings, alginate alone or in combination with PPIs may be useful for the relief of EER symptoms. Currently, because of the lack of objective diagnostic methodologies, it is difficult to come to a precise conclusion. There is a strong need for further studies in patients with these symptoms.

Long-term and/or on-demand use of alginates

Many patients receive long-term treatment following 4 to 8 weeks of initial GERD treatment to maintain adequate symptom control (79). After the cessation of treatment, in up to 75% of patients, GERD symptoms rapidly reoccur; therefore, the arranging of maintenance treatment is very important. Different maintenance treatment modalities have been defined. According to the Turkish Reflux Study Group Consensus Report definitions, there are 3 types of maintenance treatments. These are continuous treatment, intermittent treatment and on-demand treatment. In continuous treatment, patients continue to take their drugs without stopping therapy. In on-demand treatment, patients take their drugs at a standard or maintenance dosage when their symptoms occur. Finally, in intermittent treatment, patients receive a standard or maintenance dose of a drug for two to eight weeks when their symptoms recur (80).

Although randomized, controlled studies have demonstrated that the most effective drugs for the maintenance treatment of GERD are PPIs, the safety of these medications for long-term use has raised many questions (81). A recent expert review reported by the American Gastroenterology Association advised the periodic re-evaluation of the PPI dosage to detect the lowest effective dose for maintenance treatment (82). In addition to safety issues, a significant proportion of patients with GERD (25-47%) exhibit poor or moderate compliance for their prescribed PPIs (83,84). Due to the abovementioned issues, potent,

cost-effective and safe long-term maintenance strategies are necessary for some GERD patients.

In symptomatic GERD, preventing acidic flow into the esophagus is an alternative medical treatment. By creating a barrier to gastroesophageal acid exposure, alginic acid seems to be a useful alternative medical treatment for symptomatic reflux disease. Several randomized studies have demonstrated that alginate was superior to placebo or antacids for decreasing GERD symptoms. Alginate was found to be superior to a placebo or an antacid (OR: 4.42 (95% CI: 2.45-7.97)) in a recent meta-analysis. Additionally, the efficacy of alginate was comparable to that of omeprazole or H₂ receptor blockers for symptomatic GERD (OR: 0.58; 95% CI 0.27-1.22) (33). In a more recent study, Wilkison et al. (60) showed that patients receiving alginic acid had significantly higher treatment effects (evaluated with the Reflux Disease Questionnaire) for GERD symptoms than patients taking a placebo ($p<0.001$). All of these studies were short-term studies and showed that in the short-term symptomatic treatment of patients with NERD, alginates are superior to antacids and placebos and were as effective as omeprazole and H₂RAs. However, there are no studies in the literature analyzing the efficacy of alginates for maintenance therapy in GERD.

There are limited data on whether continuous treatment improves the quality of life and symptomatic recovery. Additionally, continuous treatment, especially with PPIs, raises concerns regarding safety and cost-effectiveness (80). Intermittent or on-demand therapy following symptomatic resolution after induction therapy seems to be more reasonable for patients with NERD or EE LA grade A and B disease. The purpose of on-demand treatment is the quick relief of symptoms using fast-acting drugs. To achieve this goal, alginates are theoretically a good alternative to PPIs for on-demand treatment. Because it takes hours to raise the intragastric pH above 4 after the first dose of PPIs (85), the time interval to symptom relief is shorter with alginates. When added to simulated gastric acid (e.g., 0.1 N HCl) alginate forms a floating raft-like structure within a few seconds. In an in vitro study, Washington et al showed that a liquid alginic acid formulation (500 mg Na alginate, 267 mg NaHCO₃ in 10 mL; Reckitt & Colman, UK) rapidly elevated the pH of the acid phase from 2.0 to 5.6 (86). In support of these data, in an in vivo study, Dettmar et al. (35) analyzed the time of onset of the effect of alginate, omeprazole, ranitidine and control based on the esophageal and intragastric pH and found that alginate achieved a significantly more rapid reduc-

tion in acid exposure in the esophagus than either ranitidine or omeprazole.

Studies have been performed in vitro regarding pregnancy and GERD that showed that the effect is fast and that alginates can be used in on-demand therapy. However, comparative studies do not exist in this particular group.

In conclusion, alginates can be recommended for the maintenance treatment of patients with NERD or EE LA grade A and B disease as an on-demand therapy.

The role of alginates in the step-down or cessation of PPIs

The recurrence rate of typical symptoms within six months reaches approximately 80% after the cessation of PPIs. There are two different therapeutic approaches to treating GERD in clinical practice. In the step-up approach, treatment begins with lifestyle modifications, antacids alginates and H2RAs. In step-down therapy, in contrast to the step-up approach, patients receive a PPI in the beginning of treatment, and subsequently, the treatment is stepped down to identify a regimen that allows the patient to be symptom-free (87). In the step-up approach, treatment begins with the most cost-effective strategy and the more potent, more expensive medications are used if the initial therapy fails. However, in step-down therapy, less expensive medications are used only after symptom relief has been achieved with PPIs (88,89).

There are two different studies in the literature comparing the efficacy of step-up and step-down therapies, which showed that the step-down approach was more effective than the step-up approach for relieving symptoms and resolving esophagitis in patients with GERD (87,90). However, after an initial treatment with a PPI, the recurrence of GERD symptoms occurs in the majority of the patients who are stepped down to an H2RA, and these patients need a PPI, especially those who have severe GERD (3,4). In mild or moderate GERD, it has been suggested in several reports that the tapering or cessation of PPI treatment is possible (91,92).

Observational studies have documented that long-term, especially high-dose PPI treatment, may cause some adverse events, including an increased risk for hip and spine fractures, bacterial overgrowth, *Clostridium difficile* colitis, and community-acquired pneumonia. Additionally, long-term PPI treatment is associated with high pharmacy costs (93), but it should be noted that the pharmacoeconomics might be different in developing or under-

developed countries. For patients with mild-to-moderate GERD who become symptom-free with PPI therapy, an appropriate step-down treatment approach consisting of the tapering or cessation of PPIs is essential in the long-term period.

In a recent report, it was asserted that prescribing non-PPI medications for patients with GERD may facilitate tapering or discontinuing PPI therapy. In the same report, it was implied that alginate seemed to be an attractive alternative treatment to keep patients asymptomatic during tapering or after the cessation of a PPI. The authors came to this conclusion since alginate has limited systemic absorption, creates a raft-like protective barrier to limit reflux and neutralizes the acid pocket after a meal (94). In support of this statement, a recent position paper from the Romanian Society of Neurogastroenterology reported that an alginate-antacid combination was superior to both placebos and antacids to treat mild reflux symptoms and could be used to treat persistent reflux symptoms with a PPI therapy (95). In the only study concerning the efficacy of alginate in stepping down from or off of PPIs, Murie et al. (96) showed that among patients taking an alginate suspension during the step-down/cessation of therapy, 83% of these patients successfully reduced or stopped their PPIs at the end of 1 year.

In conclusion, although there are limited data in the literature showing the role of alginate in the step down/cessation of PPIs for GERD treatment, in mild-to-moderate GERD, alginate seems to theoretically be an appropriate therapy for preventing symptom relapse during the PPI tapering and off-PPI period. We suggest the following approaches for tapering or stopping PPIs:

- Fully stop PPIs and observe patients with mild symptoms
- Taper the dose and stop
- Switch to intermittent or on-demand use with PPIs and/or alginate
- Decrease to the lowest effective dose and continue
- Stop and continue with alginate, with either continuous or on-demand treatment with alginate or another non-PPI agent

Alginates in the treatment of gastroesophageal reflux in children

Introduction

Gastroesophageal reflux (GER) in children is defined as the passage of gastric contents into the esophagus with

or without regurgitation and/or vomiting. When GER leads to troublesome symptoms and/or complications, such as esophagitis or stricture, it is considered pathologic and is referred to as GERD. In clinical practice, the differentiation of these two clinical conditions may be difficult, and there is currently no standard diagnostic tool for the diagnosis of GERD in infants and children (97).

Regurgitation ("spitting up") and GER are common in infants. Half of healthy infants from birth to 3 months old have regurgitation. Regurgitation peaks at 67% at 4 months of age and disappears in 95% of infants by 12 months of age (98). Although regurgitation is physiologic and healthy infants spontaneously recover, almost 25% of parents are concerned about this condition and seek medical care.

Pharmacological therapy is not indicated for children with GER without complications and is mostly reserved for children diagnosed with GERD. The optimal therapy for GERD is not known (97). The differences in the definition of GERD, the measures and reported outcomes among studies are another problem (99). With regard to Na alginate studies, differences are more common among the studies. In addition to the differences between the inclusion criteria and follow-up, the content of the preparations, dosages, the time of administration, and the definition of response to treatment also differ.

In alginate preparations, Na alginate may be used alone or together with magnesium (Mg) alginate and/or mannitol and/or $\text{NaHCO}_3/\text{KHCO}_3$ and/or CaCO_3 . In some formulations, Mg alginate is present without Na alginate. Alginate preparations without HCO_3^- prevent reflux by increasing the viscosity of gastric contents, whereas in the presence of HCO_3^- , alginate preparations neutralize gastric acid and form a "foam raft" in the presence of gastric acid that floats on top of the gastric contents and prevents reflux. Aluminum (Al) has been removed from alginate preparations because of the side effects (26,37,100).

Although the North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN, respectively) do not recommend the use of alginate because of the limited evidence for its efficacy in children (97), in the recently published National Institute for Health and Care Excellence (NICE) guidelines, alginates are recommended as an alternative treatment to feed-thickening agents in breastfed infants or as a trial in infants for whom symptoms persist despite conservative measures (101). Additionally, a re-

cent Cochrane review stated that there is weak evidence suggesting that Gaviscon Infant improves symptoms in infants, including those with functional reflux (100).

Table 5 summarizes the results of the studies with alginates in children.

Studies with alginate formulations

a. Alginate studies without a control group

Weldon and Robinson (102) first reported the use of Gaviscon to manage infants ranging in age from 2 weeks to 11 months with uncomplicated GER in 1972. In this open-label prospective study, 18 infants with regurgitation and vomiting received Gaviscon powder (containing alginate, Mg trisilicate, Al hydroxide gel and NaHCO_3) at a dose of $\frac{1}{2}$ to 1 tsp with a 120-mL feed. All of the infants had a good symptomatic response to the treatment. The limitations of the study were the absence of the objective diagnosis of GERD and statistical results. In 1987, Gaviscon (combined with antacids, 3-5 mL after meals) was tested as a component of a triple-therapy (milk-thickening agents plus domperidone (0.8-1.0 mg/kg/day in three divided doses)) was tested on 24 infants, all with abnormal pH recording results, who were nonresponders to milk-thickening agents and positional therapy (103). The age range was 4-12 weeks at the beginning of the study, and triple-therapy was administered 3 to 5 weeks after the beginning of the study. After 10-14 days of therapy, pH monitoring was performed. The clinical symptoms of GERD disappeared in 15 of the infants, improved in 8, and remained unchanged in 1 infant with a hiatal hernia. pH monitoring showed an improvement in 7 infants and a complete normalization in 17 infants. Unfortunately, it was impossible to determine which part of the triple-therapy was (more) effective in this study.

Le Luyer et al. (104) evaluated the efficacy and safety of alginic acid (Gaviscon suspension; Na alginate, sodium hydroxide (NaOH) and CaCO_3) at two different doses (1 to 2 mL/kg/day in divided doses after meals) in 76 children with GERD, as confirmed by pH monitoring. Irrespective of the dosage used, the frequency of regurgitation ($p < 0.00001$) and vomiting ($p = 0.01$) decreased significantly after four weeks of treatment. The tolerance was good, and no adverse effects were reported. This study showed the improvement of clinical symptoms in children with GERD who were diagnosed by pH monitoring. It is an open question whether the use of a hydroxide-containing preparation may have had an additional beneficial effect on reflux symptoms. Le Luyer et al. (105) con-

Table 5. Studies with alginates in children.

Ref#	Methods	Population	Test agent(s) and doses	Interventions	Outcomes/results	Comments
Studies without control group						
102	Open-label prospective study	18 infants (age range 2 weeks to 11 months) with regurgitation and vomiting	Gaviscon powder (alginate, Mg trisilicate, Al(OH) ₃ , NaHCO ₃) 1/2-1 tsp with 120 mL feed	Clinical observation	Vomiting resolved or reduced in all patients	No objective diagnosis of GERD. No statistical analysis
103	Open-label prospective study	24 infants (age range 4-12 weeks) with abnormal pHM results. Nonresponders to milk-thickening agents and positional therapy after 3-5 weeks	Gaviscon (combined with antacids (3-5 mL) after meals) as a component of a triple-therapy (milk-thickening agents plus domperidone-0.8-1.0 mg/kg/day in three divided doses)	Repeat pHM after 10-14 days of therapy	Clinical symptoms disappeared in 15 infants, improved in 8 infants, and remained unchanged in 1 infant with a hiatal hernia. pHM showed an improvement in 7 infants and a complete normalization in 17 infants	It was impossible to decide which part of the triple-therapy was effective in this study
104	Open-label, multicenter study	76 infants, GER confirmed by pHM	Gaviscon suspension (Na alginate, NaOH, CaCO ₃) 1 or 2 mL/kg/day, divided into doses after meals for 4 weeks	Clinical observation	Both doses of Gaviscon significantly and equally reduced regurgitation (p<0.00001) and vomiting (p=0.01), were well tolerated and caused no adverse effects	A total of 18/69 patients who underwent endoscopy had erythematous and 5 had EE. What was the effect of NaOH as an antacid?
105	Open-label prospective study	83 children with symptomatic GER (48 males, mean age 7 months, range 15 days to 57 months). All had abnormal 3-hour postprandial readings by pHM (RI>4.2%)	Na alginate 5 mL, 3 hours after a meal	3-hour postprandial pHM followed by the 2 nd 3-hour pHM after the intake of Na alginate	The RI, total number of reflux episodes, and mean duration of reflux episodes reduced significantly (p<0.00001)	Very short duration. Na alginate was administered 3 hours after the meal, was different from what is recommended.
106	Open-label	28 infants (age range 3 to 12 months) with GER diagnosed by 24-hour pHM	Gaviscon 0.5 mL/kg/dose four times a day, 20 minutes after meals	A second pHM after 2 months of treatment	Total number of refluxes, number of refluxes longer than 5 minutes and RI significantly improved after treatment (p<0.05)	-
107	Prospective, observational case-control study	43 infants (median age 68 days, range 25-306) with GER symptoms who were unresponsive to behavioral and dietetic modifications. MII-pHM; RI ≥7% and the presence of >100 MII episodes/day were considered pathologic	Mg (plus simethicone, NaHCO ₃ and fructose) or Na alginate (plus NaHCO ₃ and CaCO ₃), 1 mL/kg/day, divided over the number of meals, administered after each feeding	48-h MII-pHM (24 hours without medication followed by the second 24 hours with Mg or Na alginate)	The median number of all MII reflux (acid and non-acid) episodes was reduced (p<0.001). Proximal GER episodes decreased (p=0.007). Crying-fussiness (p=0.0012), cough (p=0.005) and regurgitation episodes (p=0.04) improved. No difference between Na and Mg alginate	Three patients were excluded because of MII-pH tracing artifacts. Potential to adapt to the presence of the probe during the second period of MII-pHM. There was no long-term follow-up

Table 5. Studies with alginates in children. (continued)

Ref#	Methods	Population	Test agent(s) and doses	Interventions	Outcomes/results	Comments
Studies compared with placebo and/or other medications						
108	DB, RC, 3-armed trial	30 children aged 4 months to 17 years. No difference in demographic, clinical characteristics and baseline pHM measures	Alginate + antacid (10 mL for infants, 20 mL for older patients) vs metoclopramide 0.17 mg/kg tid (24-hour period) vs placebo (saline 0.9%, 1 mL every 8 hours)	48-hour pHM, the first 24 hours without medication and the second 24 hours with medication/ placebo	No significant difference among the 3 groups with regard to the frequency of regurgitation episodes (episode defined as pH <4), over 24 hours and the total duration of acid reflux (minutes)	No data on adverse effects. Exact preparation of the alginate-antacid was not discussed. P values were not reported
109	DB, RC trial	20 children (mean age 28 months, range 2 to 84 months). None of the children who underwent an endoscopy had evidence of esophagitis	Gaviscon Infant (with NaHCO ₃ , 2 g) vs placebo (lactose, 2 g) in 240 mL milk for 8 days	pH monitoring at baseline and on day 8	Total number of reflux episodes, reflux episodes more than 5 minutes, RI, mean duration of reflux during sleep, the number of reflux episodes 2-hours postcibally significantly decreased in the Gaviscon group. No change in the placebo group	Difference between mean ages: Gaviscon (21 months) vs placebo (35 months). Short duration (8 days). High amount of lactose (up to 12 g/day). Adverse effects not reported
110	Open-label, parallel-design	49 children (34 males) aged 2-16 years, endoscopically documented reflux esophagitis	Gaviscon tablet (Na alginate, Al(OH) ₃ , Mg trisilicate) (24 children) vs famotidine (25 children). 1 Gaviscon tablet after meals and before bedtime or 1 mg/kg famotidine. 6 months duration	Clinical observation. Repeat endoscopy	Famotidine was superior to Gaviscon for symptomatic relief and the resolution of esophagitis	At repeat endoscopy, esophagitis was resolved in 43.4% of patients with alginate and in 41.6% of patients in the famotidine group (p>0.05); however, the improvement of the endoscopic grades induced by famotidine was significantly greater
111	Randomized parallel group	50 infants (aged 2-18 months), all bottle-fed and had GER proven on pHM (RI ≥5%)	Gaviscon Infant (1/2 sachet in 90 mL feed+ carobel) vs cisapride (0.2 mg/kg/dose x4), 1 month	Diary scores, parental evaluation and repeat pHM after 1 month	Severity score significantly improved in both groups but the difference was p>0.05. Parents' consideration was 53% better in the cisapride group and 79% in the Gaviscon+carobel group (p=0.055). pH study: no significant difference among groups	Cisapride is no longer available because of adverse effects
112	DB, RC trial	80 children (aged 1-18 months; median 4.5 months) with GER but no erosions were observed on endoscopy. Diagnosis: clinical, radiological and pHM (RI>5.2%). Patients were stratified by age (<12 months, >12 months) and RI (<10%, >10%)	Mg(OH) ₂ -Al(OH) ₃ + domperidon (group A) vs Gaviscon Infant (with Al)+domperidon (group B) vs domperidon (group C) vs placebo (group D) for 8 weeks	Clinical observation. Repeat pHM	Symptoms/pH probe: group A was superior to groups B, C, and D. pHM variables were better in group A than in the other 3 groups. The total reflux time in groups B, C, and D were not significantly different after treatment	Short-term study in young children. All children received a thickening agent

Table 5. Studies with alginates in children. (continued)

Ref#	Methods	Population	Test agent(s) and doses	Interventions	Outcomes/results	Comments
113	RC trial	36 children (median age 5.6 years, range 12 months to 12 years) with a diagnosis of GERD based on symptoms, 24-hour pHM and endoscopy	Alginate alone (2 mL/kg/day in divided doses), lansoprazole 1.5 mg/kg twice daily before meals or lansoprazole + alginate with the same doses as above	Patients underwent a 24-hour pHM at one week, symptomatic evaluation at four weeks and symptom assessment with endoscopy at eight weeks	Although a significant improvement in symptoms was noted, 24-hour pHM and endoscopy ($p < 0.01$) in the patients with EE given alginate alone and alginate and lansoprazole combination achieved significantly better symptom improvement than those in the other two groups ($p < 0.01$). The improvement in the RI in the alginate and lansoprazole group was significantly superior to that in the other two groups ($p < 0.05$)	Alginate plus lansoprazole is more effective than alginate or lansoprazole alone
114	DB, RC trial, crossover design	20 bottle-fed infants (mean age 164 days, range 34-319 days), with symptoms clinically suggestive of GERD	Gaviscon Infant (Na/Mg alginate, no HCO ₃ , 625 mg in 225 mL milk) vs placebo (mannitol+ solvito, 625 mg in 225 mL milk)	24-hour Mill-pHM (dual-channel) during which there were 6 (3+3) random administrations of study drugs	No difference regarding the median number of reflux events per hour ($p = 0.78$), median number of acid reflux events an hour ($p = 0.94$), minimum distal ($p = 0.41$) or proximal ($p = 0.23$) pH, total acid clearance time per hour ($p = 0.32$), total reflux duration per hour ($p = 0.096$), and marginally lower reflux height in the esophagus with Gaviscon Infant ($p < 0.001$)	No discussion of the group demographics (age/sex) or how the infants were recruited. Symptoms/histology not recorded. Many reflux episodes were diagnosed based on impedance not on a pH probe. Short-term study, small numbers. A volume of 225 mL of milk per feeding is not possible for a 34-day-old baby. No information about night/day distribution
116	Phase III, RC, ITT, parallel-group multicenter study	90 infants aged 0 to 12 months attending 25 general practices. Clinical diagnosis	Gaviscon Infant (Al-free, Na and Mg alginate, 225 and 87.5 mgs in each sachet, respectively; weight-adjusted dose, after meals in a volume of 5-10 mL) vs placebo	Infants reassessed after 7 and 14 days	Reduction in the number and severity of vomiting episodes ($p = 0.009$) in the previous 24 hours. Number of symptom-free days (at least 10% symptom-free days) ($p = 0.027$) Improvement in symptoms in patients on Gaviscon Infant (investigators: $p = 0.008$, parents: 0.002)	Duration of the study was 14 days. Total daily doses were unclear. Four infants from the Gaviscon Infant group and 4 infants from the placebo group were withdrawn due to adverse effects. Five children were withdrawn for a lack of efficacy (Gaviscon Infant 2, placebo 3). Compliance 71% Gaviscon Infant, 59% placebo
117	RC trial	75 patients (age range 1-10 months) with reflux and vomiting, 64 patients completed	Group A (n: 25), Mg alginate + simethicone; group B (n: 25), rice-starch-thickened formula; and group C (n: 25), control-reassurance	l-GREQ after 1 and 2 months	After 1 month, group A had a significant improvement in symptoms. After 2 months, all 3 groups of patients showed a significant reduction in symptom scores. Decrease in median symptom scores; group A vs B $p < 0.002$, A vs C < 0.0001 , B vs C < 0.001	High dropout rate. Absence of an objective diagnostic test. The amount of rice starch was high

Table 5. Studies with alginates in children. (continued)

Ref#	Methods	Population	Test agent(s) and doses	Interventions	Outcomes/results	Comments
Studies in newborns/preterm infants						
119	Open-label	34 preterm (postnatal ≥ 7 days, only breast milk). Clinical symptoms and pHM (RI $>5\%$) diagnosed	4 x 1 mL Na alginate with KHCO_3	pHM at baseline and after 48 hours	A total of 79.4% responded to treatment. Significant improvement in the number of reflux episodes, the number of reflux episodes >5 minutes, the duration of the longest reflux episode and RI. Decrease in vomiting and improvement in weight gain	The duration was short. No control group
120	Open-label	Thirty-two preterm infants with GER symptoms	Na alginate (0.25 mL/kg/dose) 4 times at alternating meals during 24-hour pHM	Twenty-four-hour pHM	Na alginate significantly decreased the number of acid GER events and the acid esophageal exposure, without any influence on non-acid GER. Decreased the number of GERs reaching the proximal esophagus	No data on reflux symptoms. Short duration
121	Open-label	Twenty-eight preterm infants with apnea, postnatal age median 35 weeks (range 32-42 weeks), on full enteral feeding	Na alginate (0.25 mL/kg with NaHCO_3) randomly given once during MII-pHM	Six-hour (3+3) recording of MII-pH + polysomnography	No decrease in apnea frequency, acid GERs and acid exposure significantly decreased but not for non-acid GER indexes. The drug reduced the number of GER episodes reaching the proximal esophagus	When alginate was given during the first 3 hours of recording, its effect may continue during the second 3 hours of recording

$\text{Al}(\text{OH})_3$: aluminum hydroxide; NaHCO_3 : sodium bicarbonate; NaOH , sodium hydroxide; CaCO_3 : calcium carbonate; $\text{Mg}(\text{OH})_2$: magnesium hydroxide; GER(D): gastroesophageal reflux (disease); pHM: pH monitoring; MII: multichannel intraluminal impedance; DB: double-blind; RC: randomized controlled; ITT: intention-to-treat.

ducted another study in 1990. In that study, 83 children with symptomatic GERD (48 males, mean age 7 months, range 15 days to 57 months) were assessed by pH monitoring. All patients showed acidic pathological GER on the 3-hour postprandial esophageal pH monitoring (the percentage of the time during which pH <4 "reflux index (RI)" $>4.2\%$), and all had a second measurement within the following 3 hours after the intake of a single (5 mL) dose of Na alginate. The RI, the total number of reflux episodes, and the mean duration of reflux episodes were significantly reduced ($p < 0.00001$). The limitations of this study were the very short duration and the administration of Gaviscon 3 hours after a meal. Most reflux episodes occur within 2 hours postprandially, and Gaviscon is most effective when it is administered 30 minutes after a meal.

Maestri (106) evaluated the effect of Na alginate (Gaviscon) in 28 children diagnosed by 24-hour pH monitoring. After the first pH recording, all patients were adminis-

tered Gaviscon (0.5 mL/kg/dose four times a day, 20 minutes after meals). After 2 months of treatment, pH was monitored a second time. The total number of refluxes, the number of refluxes longer than 5 minutes and the RI significantly improved after treatment ($p < 0.05$).

In a prospective, observational study, Salvatore et al. (107) enrolled 43 infants (median age 68 days, range 25-306) who were referred for MII-pHM because of persistent GERD symptoms that were not responsive to behavioral and dietetic modifications. All infants underwent a 48-hour MII-pHM; a baseline recording was obtained during the first 24 hours, while Mg (Mg alginate, simethicone, NaHCO_3 , and fructose) or Na alginate (Na alginate, NaHCO_3 , and CaCO_3) (both preparations were administered 1 mL/kg/day, divided over the number of feeds) was administered during the second 24 hours. Three patients were excluded because of MII-pH tracing artifacts. The median number of all MII reflux episodes ($p < 0.001$), acid

($p < 0.04$), non-acid ($p < 0.004$), proximal GER episodes ($p < 0.007$) and the bolus exposure index ($p = 0.002$) significantly improved during alginate administration, without a significant difference between Mg and Na alginate. Crying/fussiness ($p = 0.00012$), cough ($p = 0.005$) and regurgitation ($p = 0.04$) episodes all significantly improved during alginate administration. The study design by Forbes et al. (108) reduced possible confounding factors, such as feeding and awake/asleep periods. However, the infant may become adapted to the presence of the probe during the second 24-hour period, causing a normalizing effect. The clinical relevance of these differences needs to be ascertained because of the absence of long-term follow-up. This study also showed that Mg and Na alginate have the same effect profile.

Although there were no control groups and different formulations, dosages and designs were used, these studies showed that alginates may improve the clinical symptoms of GERD, such as regurgitation, vomiting, crying and fussiness and may improve the pH monitoring and/or MII-pHM parameters.

b. Comparison of alginate-based formulations with placebos and/or other medications

In 1986, Forbes et al. (108) compared Gaviscon Infant liquid (antacid+alginate) with metoclopramide (0.5 mg/kg/day in 3 doses before meals, 10 children, mean age 68 months, range six to 168) and placebo (0.9% saline, 1 mL oral every 8 hours before meals, 10 children, mean age 65 months, range four to 203) in a double-blind randomized trial. Ten children (mean age 68 months, range four to 168 months) were given Gaviscon Infant every six hours (10 mL for infants and 20 mL for older children). Two 24-hour pH recordings were made: at baseline and with treatment. There was no statistically significant difference among the three groups in regard to the number of episodes of GER or the total duration of GER during the initial 24-hour period of pH monitoring. Neither metoclopramide nor alginic acid with antacids decreased the number of the episodes of GER or the total duration of GER during the second 24-hour period of pH monitoring compared to placebo. The study design reduced possible confounding factors, such as feeding and awake/asleep periods. However, as the authors stated, an adaptation of the infant to the presence of the probe during the second 24-hour period may have had a normalizing effect. The clinical relevance of these differences need to be ascertained because of the absence of follow-up. The wide age range (4-203 months), the administration time of Gaviscon (it was not stated if Gaviscon was given before or

after each meal) and the presence antacid with alginate were the other limitations of this study.

In 1987, Buts et al. (109) obtained results that markedly contrasted with Forbes et al. (108) study. These researchers randomly assigned 20 infants and children with GER to two groups: the Gaviscon group (10 children, mean age 21 months, range two to 84 months, 2 g alginate with NaHCO_3 dissolved in 240 mL milk or in $\frac{1}{2}$ a glass of water after each meal) and the placebo group (2 g lactose sachet after each meal) (10 children, mean age 35 months, range two to 144 months). Twenty-four-hour pH monitoring was performed at baseline and on day 8, and the symptoms, which included vomiting and the number of regurgitation episodes within 24 hours, were recorded by the staff. The patients were fed every 4 hours, alternating cow's milk formula or orange juice ($\text{pH} = 4$) during pH monitoring, and during the second pH recording, one sachet was given with each serving of milk or orange juice (six times/day). Before the trial, the pH monitoring variables (the Euler-Byrne index, RI, mean duration and percentage of reflux time during sleep, total number of reflux episodes, number of reflux episodes longer than 5 minutes per 24 hours and number of reflux episodes per 2-hour postcibal periods) were abnormal in all the patients tested. An esophagogram was performed on all patients and revealed GER in 13 patients. No evidence of esophagitis was observed at endoscopic examination in the 14 patients tested. The number of episodes of regurgitation per day reported by the parents reduced by three to four times during the trial, and vomiting improved in all cases, whereas no clinical improvement was observed in the placebo group. After eight days of treatment with Gaviscon, all the pH monitoring variables significantly ($p < 0.05$) reduced by between 35% and 61% compared to the initial recorded values. In the placebo group, the changes were very small and were not significant (-9.5 to +8.2% of the initial values). The limitations of this study were the wide age range, the high dose of lactose as a placebo and the frequent feeding protocol. Although statistical results were not reported, the age of the patients in the Gaviscon group was lower than that in the placebo group. Another problem with this study was the high dose of lactose that was used as a placebo. The authors did not state that the dose was regulated according the age/weight of the patient and stated that the patients received 2 g of lactose every 4 hours. This means that a 2-month-old infant received 12 g of lactose (more than 2 g/kg/day) per day. This may have affected the results. The feeding frequency may have been another limitation. The oldest patient in the study was 12 years old, and the patients were fed every 4 hours.

In 1990 (110), alginate (0.5 g alginate) +antacid (0.1 g Al hydroxide, 0.025 g Mg trisilicate and 0.17 g NaHCO₃) (group A; 1 tablet to be chewed 30 minutes after each meal and at bedtime) was compared with famotidine (group B: 1 mg/kg before supper at 7 pm) for the treatment of endoscopically documented peptic esophagitis associated with acid reflux. Twenty-four of the 49 children (mean age 9 years, 34 males) were randomly allocated to group A, and 25 were allocated to group B. After 6 months of treatment, endoscopy was repeated. Symptoms disappeared in 43.4% of children and improved in 47.8% of children in group A and disappeared in 91.6% of those in group B ($p < 0.05$). After six months, at endoscopy, esophagitis had resolved in 43.4% of group A and in 41.6% of group B, and the difference between these two groups was not significant; however, the improvement of endoscopic grades induced by famotidine was significantly better than that of the other treatment ($p < 0.05$). Histologic examination showed healed peptic esophagitis in 52.2% of the children in group A and in 70.8% of group B ($p < 0.001$). No toxicity was observed with either treatment. The authors concluded that famotidine is superior to alginate-antacid in treating peptic esophagitis associated with acid reflux since it induced a better symptomatic response and a greater improvement of endoscopic lesions.

Greally et al. (111) compared the efficacy of Gaviscon (containing HCO₃, half a sachet in each 90 mL feed, 24 infants) plus carobel carob seed flour (1-2 scoops in each 90 mL feed) with that of cisapride (0.2 mg/kg/dose four times a day, 26 infants) in the treatment of GER in 50 bottle-fed infants (age range 2 and 18 months) with confirmed GER by esophageal pH monitoring (RI $\geq 5\%$) in a randomized, parallel-group study. Parental evaluations, diary scores for the severity of symptoms, and 24-hour pH recordings before and after one month of treatment were compared. The diary scores significantly improved in both groups, and the median change was greater in the Gaviscon plus carobel group ($p < 0.05$ and < 0.01 , respectively), but the difference between the groups was not significant. In the cisapride group, 53% of the patients were considered better by their parents, while this ratio was 79% in the Gaviscon plus carobel group ($p = 0.055$). With regard to the pH recording variables, five of 17 variables analyzed were significantly improved from the baseline in the cisapride group compared with 11/17 variables in the Gaviscon plus carobel group, but a direct comparison between the two groups of changes in each pH variable revealed no significant differences ($p > 0.05$). In 1994, Carroccio et al. (112) compared combinations

of domperidone, Maalox (Mg hydroxide/Al hydroxide) and Gaviscon Infant (with Al) in 80 infants (median 4.5 months; range one to 18 months of age) with the symptoms of reflux. Fifty of the infants had vomiting, 20 had weight loss, four had recurrent bronchopneumonia, five had prolonged crying after feeding and one had apnea. The diagnosis of GER was confirmed on the basis of radiologic (at least two reflux episodes during fluoroscopy) and 24-hour pH monitoring data (RI $> 5.2\%$). Before treatment, all patients underwent upper GI endoscopy. The patients were randomly divided into 4 groups (stratified block randomization; age less/more than 12 months and total reflux time $\leq / > 10\%$): group A, domperidone (0.3 mg/kg/dose) 15 minutes before meals + Maalox (41 g/1.73 mg/day) 1-hour and 3-hours after meals; group B, domperidone (0.3 mg/kg/dose) + Gaviscon Infant (0.7 mL/kg/dose, immediately after and 3-hours after meals); group C, domperidone (0.3 mg/kg/dose) only; and group D: placebo 1-hour and 3-hours after meals. All children receiving formula had their feeds with thickener (1% Medigel). The demographic and clinical characteristics of the groups were not different. All children were clinically evaluated and had 24-hour pH monitoring before and eight weeks after treatment. After treatment, the complete resolution of symptoms was higher in group A than in group B ($p < 0.018$), group C ($p < 0.034$), and group D ($p < 0.001$). Although there was a statistically significant improvement in several pH monitoring variables (the RI and/or the number of episodes longer than 5 minutes and/or the Jolley score) in all treatment groups, the median total reflux time and RI were significantly lower in group A than that in the other groups. The total reflux time after treatment in group B and group C were not significantly different from that in the placebo group. Clinically, the patients in group A were significantly improved compared to those in the other groups. The authors concluded that the combination of domperidone plus Mg hydroxide and Al hydroxide was more effective than the other treatments. However, the administration of a thickening agent in all groups, Medigel 1%, may have been a confounding factor for the significant improvement of the pH parameters in the placebo group.

In 2002, Borrelli et al. (113) enrolled 36 children (median age 5.6 years, range 12 months to 12 years) with a diagnosis of GERD based on symptoms, 24-hour pH monitoring and endoscopy. Participants were randomly assigned to three groups: alginate alone (2 mL/kg/day in divided doses), lansoprazole 1.5 mg/kg twice daily before meals or lansoprazole + alginate with the same doses as above. Patients with severe esophagitis received high-dose lan-

soprazole without randomization. Patients underwent 24-hour pH monitoring at one week, symptomatic evaluation at four weeks and symptom assessment with endoscopy at eight weeks. Although significant symptom improvements were noted, based on 24-hour pH monitoring and endoscopy ($p < 0.01$) in the patients with EE who received alginate alone, the alginate and lansoprazole combination achieved significantly better symptom improvement compared to that in the other two groups ($p < 0.01$). The improvement in the RI in the alginate and lansoprazole group was significantly superior to that in the other two groups ($p < 0.05$).

In 2005, 20 infants (mean age 163.5 days; range 34-319 days) who were exclusively bottle-fed and had symptoms suggestive of GER (regurgitation $> 3 \times$ /day, any amount; or $> \text{once/day}$, half a feed), underwent 24-hour MII studies and dual-channel pH monitoring (114). The infants received six random (3+3) Gaviscon Infant (625 mg in 225 mL milk, powder formulation not containing HCO_3^-) or placebo (mannitol and Solvito N, 625 mg in 225 mL) doses in a double-blind fashion. Gaviscon Infant consists of Na and Mg alginate and mannitol; it does not contain HCO_3^- . The observer interpreting the data was also blinded. In the infants that received Gaviscon Infant, only the reflux height improved, without other significant differences, when compared to the infants who received a placebo. In contrast to some studies, these results suggest that Gaviscon Infant has little effect on GER when it is assessed in objective terms. However, the dosage used in this study was lower than that recommended by the manufacturer, which may have influenced the results. Sleep and wakefulness may also affect GER episodes and may lessen the differences, as shown previously (115), and meals without and with alginate were altered, possibly inducing an ongoing effect of alginate during a drug-free meal. Additionally, the absence of HCO_3^- in the preparation that the researchers used prevented the formation of a raft, thus the treatment acted as a thickening agent only. Although it was stated that all patients consumed 225 mL milk 6 times daily (1350 mL/day), it does not seem possible for a 34-day-old baby to consume that amount of milk. There were no data on the baseline parameters or on the improvement in GERD symptoms, so no conclusions about the improvement in GERD symptoms could be made.

Miller (116) conducted a phase III, multicenter, double-blind randomized controlled study comparing Gaviscon Infant (Al-free, Na alginate 225 mg and Mg alginate 87.5 mg in each sachet) vs placebo, which included 90

infants (aged 0 to 12 months). The inclusion criteria were the presence of symptoms consistent with GER at least twice daily for the two days prior to the start of the study. The exclusion criteria were the presence of known esophageal/GI disease, weighing less than 2.5 kg or prematurity. Bottle-fed infants weighing < 4.5 kg were given one sachet in at least 115 mL of food and those who were ≥ 4.5 kg were given two sachets in at least 225 mL of food. Breastfed infants received the same amount of drug in 15 mL of water. Patients were reassessed after seven and 14 days. The improvement in symptoms and quantified vomiting/regurgitation episodes over the previous 24 hours (from none to severe (three)) were recorded. Forty-two of the patients were randomized to receive alginate, and 48 were randomized to receive placebo. There were 20 withdrawals from the study (alginate 7 and placebo 13, $p > 0.2$). The adverse events were not different in the alginate and placebo groups, and four patients in the alginate group and 7 patients in the placebo group were withdrawn from the study due to adverse events. Alginate was significantly superior to placebo in terms of the improvement in symptoms (investigators $p = 0.008$ and parents $p = 0.002$) and the number of vomiting episodes ($p = 0.009$). Alginate caused a trend in a reduction in the severity of vomiting ($p = 0.061$), and alginate achieved a significantly greater reduction in the mean severity of vomiting episodes ($p = 0.027$) and resulted in more patients having at least 10% symptom-free days ($p = 0.027$) compared to the placebo. The follow-up in this study was short, and the total daily doses were not reported. Thus, a symptom improvement may not represent an improvement in GER.

Ummarino et al. (117) compared the effect of Mg alginate plus simethicone (Gastrotuss Baby, DMG Italia SRL, Promezia, Italy; Al-free) with rice-starch-thickened formula in infants with GER. In this randomized controlled trial, full-term babies with symptoms suggestive of GER were evaluated with a validated questionnaire (Infant Gastroesophageal Reflux Questionnaire Revised-I-GERQ) and those with a symptomatic score ≥ 7 were enrolled in this study. The patients were randomized into three groups: group A (25 patients), Mg alginate plus simethicone (2.5 mL 3 times/day for infants weighing < 5 kg or 5 mL 3 times a day for those weighing > 5 kg, given 10 minutes after eating); group B (25 patients), rice-starch-thickened formula (14.3 g rice starch per 100 mL milk for infants younger than 6 months and 14.2 g per 100 mL of milk for older infants), and group C (25 patients), advice on lifestyle changes. The response was evaluated after 1 month and 2 months. Sixty-four (85.3%) of the 75 en-

rolled infants (median age 5 months; range 1-10) completed the study. After one month of treatment, group A patients showed a statistically significant improvement in symptoms compared with group B ($p < 0.03$) and group C ($p < 0.0001$) patients. The median symptom score also significantly decreased ($p < 0.02$) in group B at one month but was not significantly different in group C ($p < 0.07$). At the end of the study, although all three groups of patients showed a significant reduction in symptom scores ($p < 0.002$, $p < 0.038$, and $p < 0.03$, respectively), the median symptom score values were more significantly reduced in group A than in group B ($p < 0.002$) and group C ($p < 0.0001$) and in group B than in group C ($p < 0.001$). At the end of one month of treatment, 48% of the patients in group A, 16% of the patients in group B, and none of the patients in group C were free of symptoms.

c. Use of alginate-based formulations in neonates and preterm infants

At present, there is no consensus on the pharmacological treatment of GER in preterm newborns. The most commonly used drugs are alginate formulations, H_2RA and PPIs (118).

Atasay et al. (119) evaluated the effect of Na alginate on preterm infants. They enrolled 41 preterm infants with a clinical diagnosis of GER, and 34 (83%) of these patients had pathologic measurements on 24-hour pH monitoring. There was no significant difference between patients who did and did not have pathologic measurements in regard to gestational age, birth weight, and postnatal age and weight on the day of pH monitoring ($p > 0.05$). Four times a day, 1 mL/kg of Na alginate with $KHCO_3$ was administered to the patients with pathologic pH measurements and pH monitoring was repeated after 48 hours of treatment. The major outcomes were an improvement in the number of reflux events per 24 hours, the duration of the longest episode, the number of episodes > 5 minutes, and the RI. Twenty-seven (79.4%) of the 34 patients responded to treatment. Treatment with Na alginate significantly improved the number of episodes per 24 hours, the RI, the number of episodes > 5 minutes and the duration of the longest episode. Patients were also evaluated for vomiting and weight gain 1 week after the treatment. The frequency of vomiting decreased and weight gain improved.

Corvaglia et al. (120) evaluated the effect of sodium alginate on GER features in preterm babies by MII-pHM. Thirty-two symptomatic preterm infants underwent a 24-hour MII-pHM during which each baby was fed eight

times. Sodium alginate (0.25 mL/kg/dose) was given four times at alternating meals; drug-given (DG) vs drug-free (DF) meals. The 2nd, 4th, 6th and 8th meals were DG, whereas the remaining were DF. Sodium alginate significantly decreased the number of acid GER detected either by pH monitoring ($p = 0.002$) and MII-pHM ($p = 0.050$), as well as the acid esophageal exposure ($p = 0.030$), without any influence on non-acid GER. Furthermore, sodium alginate decreased the number of cases of GER reaching the proximal esophagus ($p = 0.030$). The use of sodium alginate in preterm infants seems to be promising because this drug decreases GER acidity and height and has the advantage of having a non-systemic method of action and a more favorable safety profile than H_2RA and PPIs. The design of this study did not allow an adequate evaluation of reflux symptoms because of the limited duration of MII-pHM.

In another study conducted by Corvaglia et al. (121) on preterm infants (gestational age ≤ 33 weeks, weight ≥ 1100 g, on full enteral feeding) with apneas related to GER. Twenty-eight preterm infants (postnatal age median 35 weeks, range 32-42 weeks) with apnea of prematurity (AOP) were studied by a six-hour MII-pHM recording and polysomnography, including two three-hour postprandial periods. Na alginate (Gaviscon 0.25 mL/kg with $NaHCO_3$) was given after a single meal, referred to as the DG meal, while the other meal was referred to as the DF meal. The DG meal was randomly chosen. Na alginate administration did not decrease the number of AOP ($p = 0.99$) events. A significant reduction in the number of acid GER ($pH < 4$) events and in acid exposure was found during DG, while the administration of Na alginate did not influence non-acid GER indexes. DG periods also significantly reduced the number of proximal GER events ($p < 0.0001$) as well as reducing the distal acid GERs detected by MII-pHM ($p = 0.003$). The reason that a drug that acts on acid GER is ineffective in reducing apneas is probably related to peculiar GER features. Recently, some authors have hypothesized that reflux triggers apnea only under certain circumstances that still remain to be identified and that only certain types of refluxed material may induce apnea: specifically, it has been stated that "the acidity, volume, or pressure of the refluxed material could determine the respiratory response".

In Corvaglia et al. (120,121) studies, meals with and without alginate were alternated, possibly inducing a carry-over effect of alginate during a drug-free meal.

The investigation and management of GER in neonatal intensive care units (NICU) widely varies. In 2017, Rossor

et al. (118) sent a questionnaire to all 207 United Kingdom neonatal units, and responses were obtained from 84% of units. To establish a diagnosis, 58% of units used a trial of treatment, and Gaviscon was the most commonly (60%) used drug followed by ranitidine (53%). Investigations including pH monitoring (24%), GI contrast studies (23%), MII-pHM (6%), abdominal ultrasonography (3%) and gastroesophageal scintigraphy (2%) were used less frequently. The thresholds for an abnormal pH study and/or MII-pHM study were also different among the units. Only two units never started antireflux medication prior to investigations, and 32% of the units started medication without investigations.

Briefly, in preterm babies, alginates decreased the number of vomiting episodes and improved weight gain (119), improved pH monitoring variables, particularly acidic reflux events (119-121), and decreased reflux events that reached the proximal esophagus (120,121). Although there is a case report showing that alginate may resolve AOP (122), Corvaglia et al's study did not show any beneficial effect of alginates on AOP (120).

The routine use of alginates in preterm infants needs to be more thoroughly studied before its routine use can be recommended in this special population.

Side effects

There are very few studies about the adverse effects of alginates in childhood. Nevertheless, alginates seem to have no severe/significant side effects. Although diarrhea, teething syndrome, nausea and vomiting, constipation, colic, fever, and acute nasopharyngitis are the most commonly reported adverse effects, their frequencies were not significantly different ($p > 0.02$) from those of placebo (116).

Na-containing formulations should be prescribed with caution to preterm babies and to people with cardiac failure, renal impairment, diarrhea and vomiting (123). Formulations containing Al may cause increased serum Al plasma concentrations (124,125). Fortunately, there are currently no Al-containing commercial formulations.

Gaviscon may rarely cause Gaviscon bezoars (gavisconoma), and the combined use of thickening agents increases this risk. In that case, the drug should be immediately stopped (126). When dehydration is likely due to excessive water loss or when there is a risk of intestinal obstruction, alginate formulations should not be used (123). HCO₃-containing formulations may cause hypokalemic

metabolic alkalosis when taken at high doses and in the presence of vomiting (127). Alginate-based agents may decrease the Ca and iron availability (128).

Conclusion

Current data suggest that alginates are moderately effective in the treatment of GER in childhood. In the majority of these studies, alginate administration improved clinical symptoms, such as regurgitation, the incidence and severity of vomiting, crying and fussiness in both studies without control groups (102-104,107) and with control groups (109-113,116,117).

Four studies showed that alginates reduce the number of refluxes that reach the proximal esophagus and the height of the refluxate in the esophagus (107,114,120,121). When alginates contain HCO₃, alginates decrease the acidity of the reflux, showing the same efficacy as acid suppressors (117). Compared to H₂RA and PPIs, alginate-based formulations are less effective for the treatment of esophagitis (37). There are many controversial studies on the effect of alginates on MII-pHM and/or pH recording parameters, and studies on children are scarce. Although there are controversial reports (108,114), alginate administration decreases the number of refluxes (particularly acidic refluxes), the RI, the number of reflux episodes lasting >5 minutes, and the duration of the longest reflux episodes (110-113,116,117).

It is hard to interpret and compare these studies; the contents and dosages of alginate formulations used in the trials, the designs and outcome parameters, and the ages of the populations are different. Most of these studies were in infants, and the natural tendency of GER to improve over time may have influenced some of the results.

Alginate is widely used in children, including neonates and premature babies, without serious adverse effects. Further well-designed studies on the effect of alginates on the clinical and laboratory characteristics of reflux are needed.

Use of alginates for the treatment of gastroesophageal reflux disease in pregnancy and lactation

Heartburn occurs frequently in pregnancy (30%-50%), and it becomes more common in the third trimester. There are several mechanisms causing GERD in pregnancies. A significant decrease in lower esophageal sphincter pressure, elevated intraabdominal pressure, increased progesterone levels and delayed intestinal transit are the leading causes of GERD in pregnancy (129).

Alginate builds a nonsystemic, strong, raft-like barrier against the reflux of acid and food into the esophagus. Since it is a nonsystemic agent, theoretically alginate appears to be a safe choice for the treatment of GERD in pregnancy. In an open-labeled multicentered study, the use of alginate for over 4 weeks resulted in satisfactory treatment endpoints, while fetal distress was observed in only 3 fetuses (130). In another two-center (South Africa and United Kingdom) prospective study, fetus-related perinatal morbidity and mortality rates were comparable to that in the normal population with alginate therapy, given at a maximum dose of 80 mL/day for 4 weeks (131). In a more recent study, alginate and antacids were compared with 50 pregnant women in each group, and no difference was found between groups in terms of the pregnancy and neonatal outcomes (132).

There are extremely limited data concerning the use of GERD drugs during the lactation period, and the data are anecdotal. Since it is not systemically absorbed, alginate was recommended for GERD treatment during the lactation period in the Turkish Reflux Study Group Consensus Report (129).

In conclusion, during pregnancy and lactation, alginate can be recommended as a first-level treatment agent.

Safety of alginates

To the best of our knowledge, to date, there has been no study in the literature that has aimed to analyze the safety of alginate as a primary study endpoint. However, there are satisfactory indirect data from efficacy studies confirming that alginate is a safe agent for the treatment of GERD.

In a placebo-controlled study, 13 adverse events occurred in 3 patients in the alginate group, and 19 adverse events were seen in 11 patients in the placebo arm. The treatments were generally well tolerated, and no serious adverse events were reported in either group (46). A low incidence of adverse events was observed in another study comparing alginate (5.4%) and omeprazole (5.5%). The severity of all adverse events was mild or moderate, and no severe adverse events were reported during the study period (44). Pouchain et al. (39) showed that omeprazole and alginate were comparable in terms of safety. At least one adverse event was reported in 12.6% of the alginate group, while it was reported in 14.2% of the omeprazole group. One severe adverse event occurred in the omeprazole group,

and there were no severe adverse events in the alginate group. In a prospective randomized study, three (4.35%) patients in the alginate group and four (6.12%) patients in the antacid group had at least one adverse event. No dosage modification was applied for the three adverse events in the alginate group, while two of the four adverse events in antacid-treated patients led to a dose reduction of the medication. No serious adverse events were reported during the entire study period (38).

In conclusion, the safety profile of alginates is comparable to that of placebo/antacid or PPIs, and according to the current literature, no serious adverse events were observed during alginate treatment.

Conclusion

In this expert opinion paper, we evaluated the different aspects of alginate treatment in patients with GERD. It is possible to conclude from the existing studies that:

1. According to the production methods, each alginate has different characteristics, and it is not possible to replace an alginate from one source with one from another source. Basic science studies showed that *Laminaria hyperborea* was able to form strong, coherent, voluminous and highly buoyant rafts compared to others.
2. Alginate has a unique mode of action, producing raft formation. The effect is fast.
3. Alginate monotherapy is a preferable option for the treatment of mild GERD symptoms.
4. In patients with severe or breakthrough symptoms in PPI-unresponsive GERD, alginates can be used in combination with PPIs to improve symptoms and to reduce reflux events.
5. Although more data are needed, the efficacy in regurgitation-dominant GERD is possibly higher with alginates.
6. Alginates have a place in the management of atypical GERD symptoms.
7. Alginate can be used either long term and/or on-demand therapy following the cessation of PPIs.
8. In the treatment of GERD in children, alginates have a proven and efficient effect and are safe.
9. Alginates can be used in pregnancy and lactation as a first-line therapy.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study was supported by Reckitt Benckiser Turkey with an unrestricted grant.

REFERENCES

- Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastro-oesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101: 1900-20; quiz 1943. [CrossRef]
- Spechler SJ, Jain SK, Tendler DA, Parker RA. Racial differences in the frequency of symptoms and complications of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2002; 16: 1795-800. [CrossRef]
- Roman S, Gyawali CP, Savarino E, et al. Ambulatory reflux monitoring for diagnosis of gastro-oesophageal reflux disease: Update of the Porto consensus and recommendations from an international consensus group. *Neurogastroenterol Motil* 2017; 29: 1-15. [CrossRef]
- El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014; 63: 871-80. [CrossRef]
- Richter JE, Rubenstein JH. Presentation and Epidemiology of Gastroesophageal Reflux Disease. *Gastroenterology* 2018; 154: 267-76. [CrossRef]
- Bor S, Mandiracioglu A, Kitapcioglu G, Caymaz-Bor C, Gilbert RJ. Gastroesophageal reflux disease in a low-income region in Turkey. *Am J Gastroenterol* 2005; 100: 759-65. [CrossRef]
- Yonem O, Sivri B, Ozdemir L, Nadir I, Yuksel S, Uygun Y. Gastroesophageal reflux disease prevalence in the city of Sivas. *Turk J Gastroenterol* 2013; 24: 303-10. [CrossRef]
- Ülkü D. Bolu ili merkezinde GÖRH prevalansı. UGH, Antalya. 2012.
- Bor S, Vardar R, Vardar E, Takmaz S, Mungan ZA. Endoscopic findings of gastroesophageal reflux disease in Turkey: Multicenter prospective study (Gorhen). *Gastroenterology* 2008; 134: 4(Suppl 1): A-600. [CrossRef]
- Bor S, Kitapcioglu G, Kasap E. Prevalence of gastroesophageal reflux disease in a country with a high occurrence of *Helicobacter pylori*. *World J Gastroenterol* 2017; 23: 525-32. [CrossRef]
- Mungan Z. Prevalence and demographic determinants of gastroesophageal reflux disease (GERD) in the Turkish general population: a population-based cross-sectional study. *Turk J Gastroenterol* 2012; 23: 323-32. [CrossRef]
- Bor S, Santaş Yüksel E. How is the gastroesophageal reflux disease prevalence, incidence, and frequency of complications (stricture/esophagitis/Barrett's esophagus/carcinoma) in Turkey compared to other geographical regions globally? *Turk J Gastroenterol* 2017; 28(Suppl 1): S4-S9. [CrossRef]
- Dent J, Becher A, Sung J, et al. Systematic Review: Patterns of Reflux-Induced Symptoms and Esophageal Endoscopic Findings in Large-Scale Surveys. *Clin Gastroenterol Hepatol* 2012; 10: 863-73.e3. [CrossRef]
- Ronkainen J, Aro P, Storskrubb T, et al. High prevalence of gastro-oesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol* 2005; 40: 275-85. [CrossRef]
- Zou D, He J, Ma X, et al. Epidemiology of symptom-defined gastroesophageal reflux disease and reflux esophagitis: The systematic investigation of gastrointestinal diseases in China (SILC). *Scand J Gastroenterol* 2011; 46: 133-41. [CrossRef]
- Ou JL, Tu CC, Hsu PI, et al. Prevalence and risk factors of erosive esophagitis in Taiwan. *J Chin Med Assoc* 2012; 75: 60-4. [CrossRef]
- Yılmaz N, Tuncer K, Tunçyürek M, Özütemiz O, Bor S. The prevalence of Barrett's esophagus, erosive esophagitis in a tertiary referral center in Turkey. *Turk J Gastroenterol* 2006; 17: 79-83.
- Kang JY. Systematic review: geographical and ethnic differences in gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2004; 20: 705-17. [CrossRef]
- Gerson LB, Shetler K, Triadafilopoulos G. Prevalence of Barrett's esophagus in asymptomatic individuals. *Gastroenterology* 2002; 123: 461-7. [CrossRef]
- Rex DK, Cummings OW, Shaw M, et al. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. *Gastroenterology* 2003; 125: 1670-7. [CrossRef]
- Shiota S, Singh S, Anshasi A, El-Serag HB. Prevalence of Barrett's Esophagus in Asian Countries: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2015; 13: 1907-18. [CrossRef]
- Toruner M, Soykan I, Ensari A, Kuzu I, Yurdaydin C, Ozden A. Barrett's esophagus: prevalence and its relationship with dyspeptic symptoms. *J Gastroenterol Hepatol* 2004; 19: 535-40. [CrossRef]
- Odemis B, Cicek B, Zengin NI, et al. Barrett's esophagus and endoscopically assessed esophagogastric junction integrity in 1000 consecutive Turkish patients undergoing endoscopy: a prospective study. *Dis Esophagus* 2009; 22: 649-55. [CrossRef]
- Loffeld RJ, van der Putten AB. Prevalence of gastroesophageal reflux disease in immigrants living in the Zaanstreek region in the Netherlands. *Dis Esophagus* 2004; 17: 87-90. [CrossRef]
- Coleman HG, Xie SH, Lagergren J. The Epidemiology of Esophageal Adenocarcinoma. *Gastroenterology* 2018; 154: 390-405. [CrossRef]
- Dettmar PW, Gil-Gonzalez D, Fisher J, et al. A comparative study on the raft chemical properties of various alginate antacid raft-forming products. *Drug Dev Ind Pharm* 2018; 44: 30-9. [CrossRef]
- Hampson FC, Farndale A, Strugala V, Sykes J, Jolliffe IG, Dettmar PW. Alginate rafts and their characterisation. *Int J Pharm* 2005; 27: 294: 137-47. [CrossRef]
- Kwiatk MA, Roman S, Fareeduddin A, Pandolfino JE, Kahrilas PJ. 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. [CrossRef]
- Kahrilas PJ, McColl K, Fox M, et al. The acid pocket: a target for treatment in reflux disease? *Am J Gastroenterol* 2013; 108: 1058-64. [CrossRef]
- Strugala V, Avis J, Jolliffe IG, Johnstone LM, Dettmar PW. The role of an alginate suspension on pepsin and bile acids - key aggressors in the gastric refluxate. Does this have implications for the treatment of gastro-oesophageal reflux disease? *J Pharm Pharmacol* 2009; 61: 1021-8. [CrossRef]
- Woodland P, Batista-Lima F, Lee C, Preston SL, Dettmar P, Sifrim D. Topical protection of human esophageal mucosal integrity. *Am J Physiol Gastrointest Liver Physiol* 2015; 308: G975-80. [CrossRef]
- Woodland P, Lee C, Duraisamy Y, Farré R, Dettmar P, Sifrim D. Assessment and protection of esophageal mucosal integrity in patients with heartburn without esophagitis. *Am J Gastroenterol* 2013; 108: 535-43. [CrossRef]
- Leiman DA, Riff BP, Morgan S, et al. Alginate therapy is effective treatment for GERD symptoms: a systematic review and meta-analysis. *Dis Esophagus* 2017; 30: 1-9. [CrossRef]
- Mitchell DR, Derakhshan MH, Robertson EV, McColl KE. The role of the acid pocket in gastroesophageal reflux disease. *J Clin Gastroenterol* 2016; 50: 111-9. [CrossRef]

35. Dettmar PW, Sykes J, Little SL, Bryan J. Rapid onset of effect of sodium alginate on gastro-oesophageal reflux compared with ranitidine and omeprazole, and relationship between symptoms and reflux episodes. *Int J Clin Pract* 2006; 60: 275-83. [CrossRef]
36. De Ruigh A, Roman S, Chen J, Pandolfino JE, Kahrilas PJ. Gaviscon Double Action Liquid (antacid & alginate) is more effective than antacid in controlling post-prandial oesophageal acid exposure in GERD patients: a double-blind crossover study. *Aliment Pharmacol Ther* 2014; 40: 531-7. [CrossRef]
37. Mandel KG, Daggy BP, Brodie DA, Jacoby HI. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. *Aliment Pharmacol Ther* 2000; 14: 669-90. [CrossRef]
38. Lai IR, Wu MS, Lin JT. Prospective, randomized, and active controlled study of the efficacy of alginic acid and antacid in the treatment of patients with endoscopy-negative reflux disease. *World J Gastroenterol* 2006; 12: 747-54. [CrossRef]
39. Pouchain D, Bigard MA, Liard F, et al. Gaviscon(R) vs. omeprazole in symptomatic treatment of moderate gastroesophageal reflux. A direct comparative randomised trial. *BMC Gastroenterol* 2012; 12: 18. [CrossRef]
40. Çelebi A, Yılmaz H. What is proton pump inhibitors unresponsiveness in gastroesophageal reflux disease? How should these cases be managed? *Turk J Gastroenterol* 2017; 28(Suppl 1): S71-S2. [CrossRef]
41. Beeley M, Warner JO. Medical treatment of symptomatic hiatus hernia with low-density compounds. *Curr Med Res Opin* 1972; 1: 63-9. [CrossRef]
42. 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. [CrossRef]
43. Goves J, Oldring J K, Kerr D, et al. First line treatment with omeprazole provides an effective and superior alternative strategy in the management of dyspepsia compared to antacid/alginate liquid: a multicentre study in general practice. *Aliment Pharmacol Ther* 1998; 12: 147-57. [CrossRef]
44. Chiu CT, Hsu CM, Wang CC, et al. Randomised 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. [CrossRef]
45. Giannini EG, Zentilin P, Dulbecco P, et al. A comparison between sodium alginate and magaldrate anhydrous in the treatment of patients with gastroesophageal reflux symptoms. *Dig Dis Sci* 2006; 51: 1904-9. [CrossRef]
46. Chatfield S. A comparison of the efficacy of the alginate preparation, Gaviscon Advance, with placebo in the treatment of gastro-oesophageal reflux disease. *Curr Med Res Opin* 1999; 15: 152-9. [CrossRef]
47. Sun J, Yang C, Zhao H, et al. Randomised clinical trial: the clinical efficacy and safety of an alginate-antacid (Gaviscon Double Action) versus placebo, for decreasing upper gastrointestinal symptoms in symptomatic gastroesophageal reflux disease (GERD) in China. *Aliment Pharmacol Ther* 2015; 42: 845-54. [CrossRef]
48. Manabe N, Yoshihara M, Sasaki A, Tanaka S, Haruma K, Chayama K. Clinical characteristics and natural history of patients with low-grade reflux esophagitis. *J Gastroenterol Hepatol* 2002; 17: 949-54. [CrossRef]
49. Manabe N, Haruma K, Ito M, et al. Efficacy of adding sodium alginate to omeprazole in patients with nonerosive reflux disease: a randomized clinical trial. *Dis Esophagus* 2012; 25: 373-80. [CrossRef]
50. Reimer C, Ng B, Smith G, Wilkinson J, Reader S, Bytzer P. Concentrated Alginate As Add-On Therapy in Gastro-Esophageal Reflux Disease (GERD) Patients With Inadequate Response to Once Daily Proton Pump Inhibitor (PPI): A Multicentre, Randomized, Double-Blind, Placebo-Controlled Pilot Study. *Gastroenterology* 2015; 148: S135-6. [CrossRef]
51. Coyle C, Crawford G, Wilkinson J, Thomas SJ, Bytzer P. 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. [CrossRef]
52. Lau J, Numans ME. 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: CD002095.
53. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. *Gut* 2012; 61: 1340-54. [CrossRef]
54. El-Serag H, Becher A, Jones R. Systematic review: persistent reflux symptoms on proton pump inhibitor therapy in primary care and community studies. *Aliment Pharmacol Ther* 2010; 32: 720-37. [CrossRef]
55. Ranaldo N, Losurdo G, Iannone A, et al. Tailored therapy guided by multichannel intraluminal impedance pH monitoring for refractory non-erosive reflux disease. *Cell Death Dis* 2017; 8: e3040. [CrossRef]
56. Kahrilas PJ, Howden CW, Hughes N. Response of regurgitation to proton pump inhibitor therapy in clinical trials of gastroesophageal reflux disease. *Am J Gastroenterol* 2011; 106: 1419-25. [CrossRef]
57. Boeckstaens G, El-Serag HB, Smout AJ, Kahrilas PJ. Symptomatic reflux disease: the present, the past and the future. *Gut* 2014; 63: 1185-93. [CrossRef]
58. Zerbib F, Duriez A, Roman S, Capdepon M, Mion F. Determinants of gastro-oesophageal reflux perception in patients with persistent symptoms despite proton pump inhibitors. *Gut* 2008; 57: 156-60. [CrossRef]
59. Thomas E, Wade A, Crawford G, Jenner B, Levinson N, Wilkinson J. 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* 2014; 39: 595-602. [CrossRef]
60. Wilkinson J, Wade A, Thomas SJ, Jenner B, Hodgkinson V, Coyle C. Randomized clinical trial: a double-blind, placebo-controlled study to assess the clinical efficacy and safety of alginate-antacid (Gaviscon Double Action) chewable tablets in patients with gastro-oesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2019; 31: 86-93. [CrossRef]
61. Akyüz F, Mutluay Soyer Ö. How is gastroesophageal reflux disease classified? *Turk J Gastroenterol* 2017; 28(Suppl 1): S10-S11. [CrossRef]
62. Cappell MS. Clinical presentation, diagnosis, and management of gastroesophageal reflux disease. *Med Clin North Am* 2005; 89: 243-91. [CrossRef]
63. Fraser-Kirk K. Laryngopharyngeal reflux: A confounding cause of aerodigestive dysfunction. *Aust Fam Physician* 2017; 46: 34-9.
64. Jaspersen D, Kulig M, Labenz J, et al. Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD Study. *Aliment Pharmacol Ther* 2003; 17: 1515-20. Erratum in: *Aliment Pharmacol Ther* 2003; 18: 355. [CrossRef]
65. Gyawali CP, Fass R. Management of Gastroesophageal Reflux Disease. *Gastroenterology*, 2018; 154: 302-18. [CrossRef]
66. Achem SR, Kolts BE, MacMath T, et al. Effects of omeprazole versus placebo in treatment of noncardiac chestpain and gastroesophageal reflux. *Dig Dis Sci* 1997; 42: 2138-45. [CrossRef]

67. Ours TM, Kavuru MS, Schilz RJ, Richter JE. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 1999; 94: 3131-8. [\[CrossRef\]](#)
68. Chang AB, Lasserson TJ, Gaffney J, et al. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev* 2005; 4: CD004823. [\[CrossRef\]](#)
69. Lieder A, Issing W. Treatment for resilient cough owing to laryngopharyngeal reflux with a combination of proton pump inhibitor and Gaviscon Advance: how we do it. *Clin Otolaryngol* 2011; 36: 583-7. [\[CrossRef\]](#)
70. Tack J. Review article: the role of bile and pepsin in the pathophysiology and treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2006; 24(Suppl 2): 10-6. [\[CrossRef\]](#)
71. Park W, Hicks DM, Khandwala F, et al. Laryngopharyngeal reflux: prospective cohort study evaluating optimal dose of proton-pump inhibitor therapy and pretherapy predictors of response. *Laryngoscope* 2005; 115: 1230-8. [\[CrossRef\]](#)
72. Williams RB, Szczesniak MM, Maclean JC, et al. Predictors of outcome in an open label, therapeutic trial of high-dose omeprazole in laryngitis. *Am J Gastroenterol* 2004; 99: 777-85. [\[CrossRef\]](#)
73. Vaezi MF, Richter JE, Stasney CR, et al. Treatment of chronic posterior laryngitis with esomeprazole. *Laryngoscope* 2006; 116: 254-60. [\[CrossRef\]](#)
74. Hom C, Vaezi MF. Extra-esophageal manifestations of gastro-oesophageal reflux disease: diagnosis and treatment. *Drugs* 2013; 73: 1281-95. [\[CrossRef\]](#)
75. Washington N. Investigation into the barrier action of an alginate gastric reflux suppressant, Liquid Gaviscon. *Drug Invest* 1990; 2: 23-3. [\[CrossRef\]](#)
76. McGlashan JA, Johnstone LM, Sykes J, Strugala V, Dettmar PW. The value of a liquid alginate suspension (Gaviscon Advance) in the management of laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol* 2009; 266: 243-51. [\[CrossRef\]](#)
77. Tseng WH, Tseng PH, Wu JF, et al. Double-blind, placebo-controlled study with alginate suspension for laryngopharyngeal reflux disease. *Laryngoscope* 2018; 128: 2252-60. [\[CrossRef\]](#)
78. Wilkie MD, Fraser HM, Raja H. Gaviscon Advance alone versus co-prescription of Gaviscon Advance and proton pump inhibitors in the treatment of laryngopharyngeal reflux. *Eur Arch Otorhinolaryngol* 2018; 275: 2515-21. [\[CrossRef\]](#)
79. Dean BB, Gano AD Jr, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004; 2: 656-64. [\[CrossRef\]](#)
80. Bor S, Kalkan İH. Medical treatment of gastroesophageal reflux disease. *Turk J Gastroenterol* 2017; 28(Suppl 1): S48-S52. [\[CrossRef\]](#)
81. Gyawali CP. Proton Pump Inhibitors in Gastroesophageal Reflux Disease: Friend or Foe. *Curr Gastroenterol Rep* 2017; 19(9): 46. [\[CrossRef\]](#)
82. Freedberg DE, Kim LS, Yang YX. 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. [\[CrossRef\]](#)
83. Metz DC, Inadomi JM, Howden CW, van Zanten SJ, Bytzer P. On-demand therapy for gastroesophageal reflux disease. *Am J Gastroenterol* 2007; 102: 642-53. [\[CrossRef\]](#)
84. Domingues G, Moraes-Filho JP. Noncompliance is an impact factor in the treatment of gastroesophageal reflux disease. *Expert Rev Gastroenterol Hepatol* 2014; 8: 761-5. [\[CrossRef\]](#)
85. Çelebi A, Aydın D, Kocaman O, Konduk B, Senturk O, Hulagu S. Comparison of the effects of esomeprazole 40 mg, rabeprazole 20 mg, lansoprazole 30 mg, and pantoprazole 40 mg on intragastric pH in extensive metabolizer patients with gastroesophageal reflux disease. *Turk J Gastroenterol* 2016; 27: 408-14. [\[CrossRef\]](#)
86. Washington N. *Antacids and Anti-Reflux Agents*. BocaRaton, FL, USA: CRC Press Inc., 1991: 215.
87. Katsanos KH, Tasolambrou C, Christodouloupoulou A, et al. Comparison of the step down disease (GERD): Results of a randomized open-label pilot study with omeprazole in Northwest Greece. *Ann Gastroenterol* 2003; 16: 138-50.
88. Eggleston A, Wigerinck A, Huijghebaert S, Dubois D, Haycox A. Cost-effectiveness of treatment for gastro-oesophageal reflux disease in clinical practice: a clinical database analysis. *Gut* 1998; 42: 13-6. [\[CrossRef\]](#)
89. Hixson L J, Kelley CL, Jones WN, Tuohy CD. Current trends in the pharmacotherapy for gastroesophageal reflux disease. *Arch Intern Med* 1992; 152: 717-23. [\[CrossRef\]](#)
90. Habu Y, Maeda K, Kusuda T, et al. "Proton-pump inhibitor-first" strategy versus "step-up" strategy for the acute treatment of reflux esophagitis: a cost-effectiveness analysis in Japan. *J Gastroenterol* 2005; 40(11): 1029-35. [\[CrossRef\]](#)
91. Vigneri S, Termini R, Leandro G, et al. A comparison of five maintenance therapies for reflux esophagitis. *N Engl J Med* 1995; 333: 1106-10. [\[CrossRef\]](#)
92. Gough AL, Long RG, Cooper BT, et al. Lansoprazole versus ranitidine in the maintenance treatment of reflux oesophagitis. *Aliment Pharmacol Ther* 1996; 10: 529-39. [\[CrossRef\]](#)
93. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected]. *Am J Gastroenterol* 2009; 104(Suppl 2): S27-S32. [\[CrossRef\]](#)
94. Kim J, Blackett JW, Jodorkovsky D. Strategies for Effective Discontinuation of Proton Pump Inhibitors. *Curr Gastroenterol Rep*. 2018;20(6):27. [\[CrossRef\]](#)
95. Surdea-Blaga T, Băncilă I, Dobru D, et al. Mucosal Protective Compounds in the Treatment of Gastroesophageal Reflux Disease. A Position Paper Based on Evidence of the Romanian Society of Neurogastroenterology. *J Gastrointestin Liver Dis*. 2016; 25:537-546. [\[CrossRef\]](#)
96. Murie J, Allen J, Simmonds R, de Wet C. 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.
97. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2018; 66: 516-54. [\[CrossRef\]](#)
98. Nelson SP, Chen EH, Syniar GM, et al. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. *Pediatric Practice Research Group. Arch Pediatr Adolesc Med* 1997; 151: 569-72. [\[CrossRef\]](#)
99. Singendonk MMJ, Rexwinkel R, Steutel NF, et al. Development of a Core Outcome Set for Infant Gastroesophageal Reflux Disease. *J Pediatr Gastroenterol Nutr* 2019; 68: 655-61. [\[CrossRef\]](#)
100. Tighe M, Afzal NA, Bevan A, et al. Pharmacological treatment of children with gastro-oesophageal reflux. *Cochrane Database Syst Rev* 2014; 11: CD008550. [\[CrossRef\]](#)
101. Davies I, Burman-Roy S, Murphy MS; Guideline Development Group. Gastro-oesophageal reflux disease in children: NICE guidance. *BMJ* 2015; 350: g7703. [\[CrossRef\]](#)
102. Weldon AP, Robinson MJ. Trial of Gaviscon in the treatment of gastro-oesophageal reflux in infancy. *Aust Paediatr J* 1972; 8: 279-81. [\[CrossRef\]](#)

103. Vandenplas Y, Sacre-Smiths L. Gastro-oesophageal reflux in infants: Evaluation of treatment by pH monitoring. *Eur J Pediatr* 1987; 146: 504-7. [CrossRef]
104. Le Luyer B, Mougnot JF, Mashako L, et al. Multicenter study of sodium alginate in the treatment of regurgitation in infants. *Ann Pediatr* 1992; 39: 635-40.
105. Le Luyer B, Mougnot JF, Mashako L, et al. Pharmacologic efficacy of sodium alginate suspension on gastro-oesophageal reflux in infants and children. *Arch Fr Pediatr* 1990; 47: 65-8.
106. Maestri L. Treatment with sodium alginate of gastroesophageal reflux disease in childhood: efficacy and tolerance assessment. *Pediatr Med Chir* 2001; 23: 187-9.
107. Salvatore S, Ripepi A, Huysentruyt K, et al. The Effect of Alginate in Gastroesophageal Reflux in Infants. *Paediatr Drugs* 2018; 20: 575-83. [CrossRef]
108. Forbes D, Hodgson M, Hill R. The effects of Gaviscon and metoclopramide in gastroesophageal reflux in children. *J Pediatr Gastroenterol Nutr* 1986; 5: 556-9. [CrossRef]
109. Buts JP, Barudi C, Otte JB. Double-blind controlled study on the efficacy of sodium alginate (Gaviscon) in reducing gastroesophageal reflux assessed by 24 h continuous pH monitoring in infants and children. *Eur J Pediatr* 1987; 146: 156-8. [CrossRef]
110. Oderda G, Dell'Olio D, Forni M, et al. Treatment of childhood peptic oesophagitis with famotidine or alginate-antacid. *Ital J Gastroenterol* 1990; 22: 346-9.
111. Greally P, Hampton FJ, MacFadyen UM, et al. Gaviscon and carobel compared with cisapride in gastro-oesophageal reflux. *Arch Dis Child* 1992; 67: 618-21 [CrossRef]
112. Carroccio A, Iacono G, Montalto G, et al. Domperidone plus magnesium hydroxide and aluminium hydroxide: a valid therapy in children with gastroesophageal reflux. *Scand J Gastroenterol* 1994; 29: 300-4. [CrossRef]
113. Borrelli O, Rea P, De Mesquita B, et al. Efficacy of combined administration of an alginate formulation (Gaviscon) and lansoprazole for children with gastroesophageal reflux. *Ital J Pediatr* 2002; 28: 304-9.
114. Del Buono R, Wenzl TG, Ball G, et al. Effect of Gaviscon Infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH. *Arch Dis Child* 2005; 90: 460-3. [CrossRef]
115. Cresi F, Savino F, Marinaccio C, et al. Gaviscon for gastro-oesophageal reflux in infants: a poorly effective treatment? *Arch Dis Child* 2006; 91: 93. [CrossRef]
116. Miller S. Comparison of the efficacy and safety of a new aluminium-free paediatric alginate preparation and placebo in infants with recurrent gastro-oesophageal reflux. *Curr Med Res Opin* 1999; 15: 160-8. [CrossRef]
117. Ummano D, Miele E, Martinelli M, et al. Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants. *J Pediatr Gastroenterol Nutr* 2015; 60: 230-5. [CrossRef]
118. Rossor T, Andradi G, Bhat R, et al. Investigation and management of gastro-oesophageal reflux in United Kingdom neonatal intensive care units. *Acta Paediatr* 2018; 107: 48-51. [CrossRef]
119. Atasay B, Erdeve O, Arsan S, et al. Effect of sodium alginate on acid gastroesophageal reflux disease in preterm infants: a pilot study. *J Clin Pharmacol* 2010; 50: 1267-72. [CrossRef]
120. Corvaglia L, Aceti A, Mariani E, et al. The efficacy of sodium alginate (Gaviscon) for the treatment of gastro-oesophageal reflux in preterm infants. *Aliment Pharmacol Ther* 2011; 33: 466-70. [CrossRef]
121. Corvaglia L, Spizzichino M, Zama D, et al. Sodium Alginate (Gaviscon) does not reduce apnoeas related to gastro-oesophageal reflux in preterm infants. *Early Hum Dev* 2011; 87: 775-8. [CrossRef]
122. Bilgin H, Eren A, Kara S. Gaviscon and domperidon responsive apnea episodes associated with gastro-oesophageal reflux disease in twins. *Asia Pac J Clin Nutr* 2015; 24: 753-5.
123. Keady S. Update on drugs for gastro-oesophageal reflux disease. *Arch Dis Child Educ Pract Ed*. 2007; 92: ep114-8. [CrossRef]
124. Woodard-Knight L, Fudge A, Teubner J, et al. Aluminium sorption and antacid therapy in infancy. *J Paediatr Child Health* 1992; 28: 257-9. [CrossRef]
125. Tsou VM, Young RM, Hart MH, et al. Elevated plasma aluminium levels in normal infants receiving antacids containing aluminum. *Pediatrics* 1991; 87: 148-51.
126. Hewitt GJ, Benham ES. A complication of Gaviscon in a neonate - 'the Gavisconoma'. *Aust Paediatr J* 1976; 12: 47-8. [CrossRef]
127. Gawarammana IB, Coburn J, Greene S, et al. Severe hypokalaemic metabolic alkalosis following ingestion of gaviscon. *Clin Toxicol* 2007; 45: 176-8. [CrossRef]
128. Bosscher D, Van Caillie-Bertrand M, Deelstra H. Effect of thickening agents, based on soluble dietary fiber, on the availability of calcium, iron, and zinc from infant formulas. *Nutrition* 2001; 17: 614-8. [CrossRef]
129. Dağlı Ü, Kalkan İH. Treatment of reflux disease during pregnancy and lactation. *Turk J Gastroenterol* 2017; 28(Suppl 1): S53-S56. [CrossRef]
130. Briggs GG, Freeman RY, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. Baltimore, USA: William and Wilkins, 2002.
131. Strugala V, Bassin J, Swales VS, Lindow SW, Dettmar PW, Thomas EC. Assessment of the Safety and Efficacy of a Raft-Forming Alginate Reflux Suppressant (Liquid Gaviscon) for the Treatment of Heartburn during Pregnancy. *ISRN Obstet Gynecol* 2012; 2012: 481870. [CrossRef]
132. Meteerrattanapipat P, Phupong V. Efficacy of alginate-based reflux suppressant and magnesium-aluminium antacid gel for treatment of heartburn in pregnancy: a randomized double-blind controlled trial. *Sci Rep* 2017; 7: 44830. [CrossRef]