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Review Article

Expert consensus on the multifaceted utility of alginates in addressing diverse manifestations of acid reflux

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ABSTRACT

Gastroesophageal reflux disease (GERD) is one of the most frequent reasons for seeking outpatient gastroenterology consultations. Current professional guidelines advocate the use of proton pump inhibitors (PPIs) as the primary medical approach to manage GERD. However, PPIs may not be as effective, especially for certain patients like those with non-erosive reflux disease (NERD). An alternative strategy for addressing symptomatic GERD involves obstructing the flow of acidic refluxate. Alginate-based pharmaceutical formulations have proven effective in alleviating symptoms of acid reflux for many years and provide rapid relief of symptoms with a long duration of action. Alginic acid derivatives, or alginates, combat acid reflux through a unique mechanism: they create a physical barrier that displaces the post-prandial acid pocket. Alginates have recently garnered renewed interest for promoting symptomatic relief especially when employed alongside antacids or PPIs. Here, the role of alginates is reviewed in the treatment of various profiles of acid reflux, including post-prandial acid reflux, nocturnal GERD, refractory GERD, and GERD during pregnancy, along with the opinion of expert gastroenterologists on the same. The experts believed that not all alginate formulations are equivalent and raft strength is the most important physicochemical property to be considered while selecting the alginate-based product. The physicochemical properties of the rafts eventually impact their effectiveness in relieving symptoms in clinical settings.

Keywords: Alginates, GERD, Regurgitation, Nocturnal GERD, Refractory GERD, India

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when there is a retrograde flow of stomach contents back into the esophagus, resulting in distressing symptoms, such as regurgitation, heartburn, and pain in chest.[1,2] In severe cases, it can lead to substantial morbidity, a diminished quality of life, and increased work absenteeism. If left untreated, GERD can progress to more severe complications, including peptic stricture, Barrett's esophagus, and even esophageal adenocarcinoma.[2] GERD is one of the most prevalent conditions seen in clinical practice of gastroenterologists, with prevalence ranging from 7.6% to 30% in India.[3,4] Among the Indian states, Chennai has the highest prevalence of GERD patients (28.5%) while Pondicherry has least (5.02%).[2] Prevalence of GERD is slightly higher in men compared to women.[1]

While not life-threatening and associated complications are rare, several patients affected with GERD report substantial morbidity and impaired quality of life.[5] According to American college of gastroenterology (ACG) recommendations, if symptoms of heartburn and regurgitation persist after an 8-week course of once-daily PPIs, esophagogastroduodenoscopy (EGD) is recommended to confirm presence of GERD.[6] In treatment of individuals with mild to moderate GERD, it is crucial to advise dietary and lifestyle modifications, with a focus on abstaining from meals at least 3 hours before bedtime.[7]

Various pharmacological treatment options are available for the treatment of GERD, and PPIs are considered the cornerstone.[8-10] However, prolonged use of PPI has been linked to adverse events like reduced magnesium and vitamin B12 levels, rebound acid secretion, and an augmented risk of diarrhoea.[11] Furthermore, in some patients with GERD symptoms, particularly those with NERD, the efficacy of PPIs in suppressing gastric acid may be less pronounced.[12]Alternative medications, such as H2RAs, are recommended for short-term use in uncomplicated GERD cases. While generally well-tolerated, H2RAs may produce mild side effects like drowsiness, headache, fatigue, constipation, or diarrhea.[13] Regular use of H2RA may lead to tachyphylaxis, which can restrict their effectiveness as a long-term treatment for GERD symptoms.[13] Given these challenges, there is an urgent need for safer and more effective treatment options for GERD, especially for patients with NERD and those unresponsive to traditional PPI therapy. Table 1 outlines the currently employed drugs for targeting GERD with their possible mode of actions.

Table 1: Available treatment options for managing GERD.[9,14,15]

Drugs	Mode of action
PPI	They inhibit the last stage of hydrochloric acid secretion by deactivating H+/K+ATPase
H2Ras	They reduce stomach acid production by competitively and reversibly blocking histamine H2-receptors
Prokinetics	These medications can boost the removal of refluxed content from the esophagus by promoting effective peristalsis and speeding up gastric emptying
P-CABs	They contest with potassium ions, causing a selective and dose-dependent reversible inhibition of the proton pump
Mucosal protectants	They hinder the movement of gastric acid and pepsin through the esophagus mucosa, preventing the erosive effects of pepsin
Antacids	They neutralize excess hydrochloric acid in gastric juice
Alginates	They create a resilient and buoyant raft, physically hindering the reflux of stomach contents into the esophagus

The Southeast Asian (SEA) consensus recommends the use of alginates as first line treatment for mild to moderate GERD.[7] Alginates are manufactured from naturally occurring brown algae (seaweed). Alginates are drugs that have been present for the past few decades but the scientific evidence for its usage in GERD is available only from the past few years.[8] When alginates interact with antacids such as sodium bicarbonate and calcium carbonate, they create a resilient and buoyant alginate raft. This helps mitigate acid reflux and alleviate heartburn symptoms and GERD by establishing a physical barrier. The raft forming capacity of the alginates depends on the seaweed species and the part of the seaweed that it is extracted from. Alginates with very low molecular weight and high gel strength are the most suitable candidates for the generation of an effective reflux response.[8] Variations in alginate and antacid compositions among alginate-based products in the Indian market leads to significant differences in raft formation, strength, and durability. Savla et al suggests that the interaction between alginate and antacids plays a crucial role in shaping the physicochemical properties of these rafts, ultimately impacting their effectiveness in relieving GERD symptoms in clinical settings.[14]

Various clinical studies have documented the use of alginates in different profiles of acid reflux.[15] Alginates alone can effectively manage mild GERD symptoms.[16] Alginates in combination with antacid also demonstrated efficacy in treating GERD with regurgitation and heartburn symptoms.[17] Alginate-based antacids offer a rapid onset of relief provided by antacids along with a longer duration of relief from heartburn and acid reflux symptoms as compared to antacids alone.[16] Combining PPIs with alginates also proves beneficial in alleviating reflux symptoms in individuals who are unresponsive to PPIs.[18] These raft-forming compounds are both effective and safe for use in children and pregnant women.[19,20] These observations are supported by the insights gleaned from focus group discussions involving 48 gastroenterologists, who provided their expert opinions on the matter, which are included in this review. Thus, this review aims to provide a comprehensive overview of alginate-based approaches to the management of various acid reflux profiles such as postprandial reflux, nocturnal GERD, refractory GERD, GERD during pregnancy, shedding light on their potential as innovative and safer alternatives to traditional treatments.

POST-PRANDIAL REFLUX AND THE ROLE OF ALGINATES

Heightened acid reflux following meals is a distinctive feature of GERD, with the "acid pocket" implicated in causing post-prandial acid reflux in affected patients. The identification of the "acid pocket" has emerged from the disparity between gastric pH and refluxate pH following meals. The acid pocket functions as a reservoir for gastroesophageal reflux containing unbuffered gastric acid that has evaded the neutralizing effects of food. This accumulation occurs in the proximal stomach following meals.[21] The occurrence of post-prandial gastroesophageal

reflux may be linked to an elevation in the frequency of transient lower esophageal sphincter relaxations (TLESRs), a phenomenon augmented in the majority of GERD patients and associated with swallow-induced lower esophagus sphincter (LES) relaxation and lower LES pressures.[22] Moreover, post prandial reflux is also frequently associated with phreno-esophageal ligament and crural diaphragm pathology.[23] According to the study conducted by Kahrilas et al the existence of an acid pocket in the postprandial phase represents a promising target for GERD treatment.[21]

Alginate-based therapeutic formulations commonly consist of three key components: sodium alginate, sodium bicarbonate ($NaHCO_3$), and calcium carbonate ($CaCO_3$). When exposed to the acidic conditions of the stomach, these elements interact to create a resilient and buoyant alginate raft.[8] The strength of the raft is influenced by the origin of the alginates and the calcium carbonate content. The capacity of calcium to enhance raft strength is attributed to its ability to cross-link alginic acid polymers, enabling the gel to adopt a robust "eggbox" structure with inherent strength (Figure 1).[24]

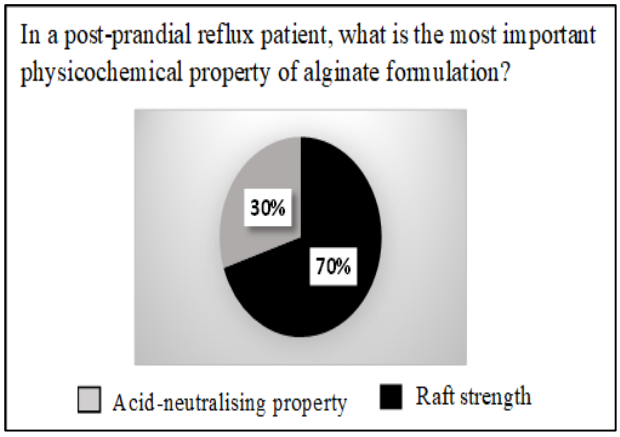

Figure 1: Most important physicochemical property of alginate in post-prandial reflux patients.

Unlike antacids and PPIs, alginate-based reflux suppressants possess the unique ability to displace the acid pocket away from the gastroesophageal junction by forming a physical barrier, thereby combating post-prandial reflux.[8] A study by Rohof et al revealed that an alginate-antacid combination significantly decreases acid reflux episodes, enhances time to acid reflux and keeps the acid pocket beneath the diaphragm in a larger number of patients as compared to antacids.[25] Another study by Kwiatek et al demonstrated that the alginate-antacid formulation has the potential to eliminate the problematic "acid pocket" observed in GERD patients, primarily by forming an alginate "raft" that dislocates gastric contents away from the esophagogastric junction (EGJ). These findings strongly indicate that the alginate-antacid formulation could serve as a well-targeted therapy for post-prandial GERD management.[26]

Expert opinion

In clinical practice, 78% of the panelists advocate for PPIs as the primary pharmacological approach for managing acid reflux. Experts also discussed that addition of acid reflux suppressant and neutralizer will be effective in patients with post-prandial reflux, especially those who are unresponsive to PPIs. Alginates can be a valuable component in GERD management, especially for mild cases where symptoms are limited to post-prandial reflux or mild to moderate regurgitation (Figure 2). In more severe instances, PPI treatment is recommended, but its duration should ideally not extend beyond 3-4 months to avoid dependency. The use of alginates being an inert substance with purely physical action, can be employed to reduce the need for PPIs. Furthermore, if symptoms are effectively controlled by using only alginate treatment, it is advised to gradually discontinue PPIs, as alginates presents a suitable alternative for long-term use.

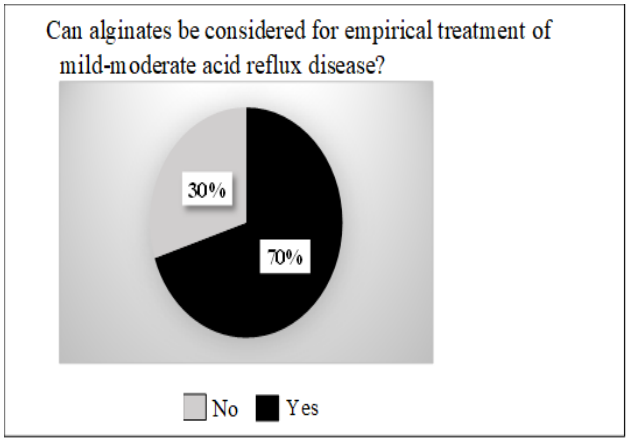

Figure 2: Alginates can be considered as an option for the empirical treatment of mild to moderate acid reflux disease.

Majority of the panelists (70%) prioritize raft strength as the foremost physicochemical characteristic of an antacid-alginate formulation, underscoring its importance in efficacy. Furthermore, a notable 85% of the panelists assert that not all alginate formulations are equivalent, indicating recognition of variations within this category. This observation was based on an in-vitro study comparing six alginate-based raft-forming products in the Indian market demonstrating that raft strengths of only two products were above the British pharmacopoeia specification of not less than 7.5 g. The strengths of the rafts varied significantly from the lowest being 1.1 g to the highest raft strength of 14 g. The study results also revealed that all the products significantly differed with regards to their duration of neutralization of gastric acid (21-88 minutes) and indicated that absorbent rafts with optimum porosity can effectively neutralize the gastric acid and prolong the duration of neutralization.[16] Moreover, an equal percentage of 85% of the panelists advocate for higher calcium carbonate content in alginate-antacid combinations, suggesting a consensus on its

potential therapeutic advantages for acid reflux symptoms such as heartburn. These insights collectively illustrate the nuanced perspectives and preferences within the gastroenterological community regarding the treatment and formulation strategies for addressing acid reflux. Experts also mention that after taking alginates, it is important to wait for 2 hours before consuming other medications to ensure their effectiveness.

NOCTURNAL GERD

Nocturnal GERD (NGERD) is referred to as the condition when an individual experiences heartburn and regurgitation during the night. Those with NGERD often have disrupted sleep, reduced quality of life, and lower work productivity compared to those without it.[27] Nocturnal acid reflux syndrome can occur in patients without apparent symptoms such as chest pain or sleep disturbances, emphasizing the importance of accurately diagnosing nocturnal reflux.[28] The pathophysiology of NGERD mainly includes no primary peristalsis, decreased triggers for secondary peristalsis, delayed gastric emptying, and the effect of gravity.[29] Although nocturnal acid reflux is less common than daytime incidents, it is associated with more severe outcomes due to the prolonged acid clearance time, which means having a greater degree of acid mucosal contact for each reflux event. This extended duration of the acid mucosal contact enables the back diffusion of hydrogen ions into the esophageal mucosa, leading to esophageal injury.[28] This phenomenon contributes to disrupted sleep by GERD-induced conscious arousal. In a study conducted by Fornari et al analysis of impedance pH tracings revealed that nocturnal weakly acid reflux is equally prevalent as acid reflux in GERD.[30] Data from multiple studies indicates that a significant percentage of patients with GERD experience night-time heartburn, with estimates ranging from 47% to 79%.[27,29] The risk factors for NGERD include increased body mass index (BMI), snoring, daytime sleepiness, insomnia, hypertension, asthma, and the use of benzodiazepines.[27] Patients with co-morbidities such as asthma are more susceptible to reflux disease and tend to develop dental caries, dry cough, or disturbed sleep.[31]

Nocturnal acid breakthrough (NAB) is characterized as the medical condition where the intra-gastric pH remains below 4 for a continuous duration of at least 60 minutes during the night-time in individuals using PPIs.[32] This phenomenon is highly prevalent, affecting up to 80% of patients who are on a twice-daily PPI regimen.[33] Initiating lifestyle and dietary modifications stands as the initial protocol for individuals with NGERD. Specific measures, including raising the head of the bed and opting for a left lateral sleeping position, have demonstrated efficacy in improving nocturnal reflux. Refraining from consuming meals late at night (within 3 hours of bedtime) has been proven to alleviate nighttime GERD-related symptoms.[34] PPIs are highly effective in alleviating symptoms of NGERD and improving parameters related to sleep quality. However, the primary function of PPIs is to reduce stomach acid rather than addressing reflux directly. Doubling the PPI dosage has demonstrated improvements in symptoms related to GERD and a reduction in sleep disturbances.[34] The ACG advises against bedtime use of PPIs for NGERD and hence must be administered at 6 P.M.[6] In cases where PPI treatment is unsuccessful, H2RAs are often administered at bedtime. Furthermore, incorporating alginate into existing PPI therapy contributes to better control of night-time symptoms.[35]

Patients with severe night-time GERD experience heightened regurgitation. Multiple studies have demonstrated that alginates are significantly more effective than both placebo and antacids in terms of relieving symptoms, whereas possess comparable efficacy to PPIs.[35,36] A study conducted by Chiu et al reported that sodium alginate is equally effective as Omeprazole in alleviating symptoms among individuals with NERD.[37] Another study by Manabe et al demonstrated that sodium alginate when combined with omeprazole fostered better complete symptom resolution compared to Omeprazole alone in patients with NERD.[38]

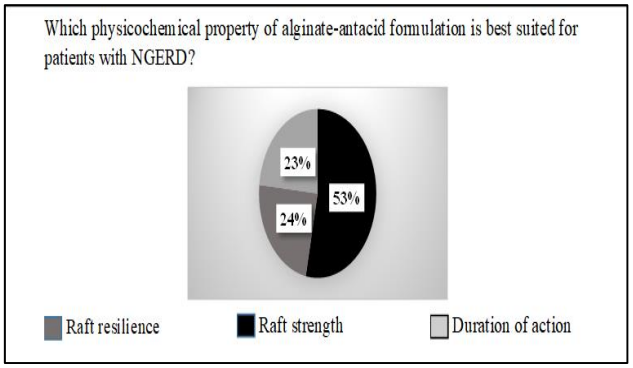

Figure 3: Physicochemical property of alginate-antacid best suited for NGERD patients.

Expert opinion

To optimize the treatment of night-time GERD, a low dose of alginates (initially 10 mL) can be combined with a low dose of PPIs during the night. This dose can later be increased to 20 mL to facilitate the gradual reduction and discontinuation of PPIs. A low-dose hypnotic medication may also aid in discontinuing PPIs and alginates in some cases. For NGERD, it is important to prescribe alginates after a meal to prevent the raft from disrupting. Alginates can be taken at bedtime for symptom relief and can be administered up to 4 times a day. The continued use of alginates in the treatment of NGERD is primarily attributed to enhanced patient compliance. 53% of the panelists endorsed raft strength as the most suitable physicochemical characteristic of alginate-antacid formulations for patients with NGERD (Figure 3). Future studies with higher concentrations of alginates and a twice-daily dosing regimen have the potential to provide

additional insights, improving the management of patients with NGERD.

REFRACTORY GERD IN PATIENTS ON PPI

Current guideline recommendations advise using acid-suppressive therapy, specifically PPIs, as the primary therapeutic option for managing GERD. PPIs inhibit the secretion of gastric acid and significantly contribute to the healing of the esophageal mucosa. However, despite their high efficacy, around 30% of patients may still experience GERD-like symptoms even with proper PPI dosage. For individuals who are refractory to PPIs or exhibit alarm symptoms such as dysphagia, weight loss, vomiting, odynophagia, or abdominal pain, further evaluation is necessary.[39] The main etiologies for refractory GERD include poor adherence to treatment, non-compliance, residual acid, rapid metabolism of PPIs, and factors unrelated to GERD.[40] Pathophysiological mechanisms contributing to refractory GERD involve heightened TLESR, the presence of a hiatal hernia, a hypotensive LES, diminished esophageal contractility, augmented mucosal permeability, persistent esophageal acid exposure despite on double dose of PPI, and delayed gastric emptying.[41] The diagnosis of refractory GERD involves an initial 8-week double dose of PPI therapy for patients experiencing concerning symptoms, despite using a single-dose PPI. If there is an inadequate response to the double-dose regimen as well, patients should undergo assessment for erosive disease using EGD or evaluation of elevated acid exposure time and/or reflux burden using pH impedance testing.[41]

An adequate management of GERD involves ensuring adherence to treatment, considering options of doubling, or escalating the PPI dosage, modifying treatment with alternative PPI formulations, splitting the PPI dose for patients with NGERD, transitioning to a cytochrome P450 (CYP)-independent PPI modality, or altering the PPI-molecule to assess and monitor the treatment response.[42] Non-pharmacological management for refractory GERD consists of lifestyle modifications: weight loss, adopting fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP)-based diet, posture correction, and discontinuing smoking, alcohol, or caffeine intake. Pharmacological management for persisting acid reflux includes optimizing PPI therapy and/or adding mucosal protective agents or alginates and/or short H2RAs course and/or potassium competitive acid blockers (P-CABs). For managing persisting weakly acid reflux, Baclofen or Sucralfate or alginates are generally recommended. Surgical options include laparoscopic anti-reflux surgery, esophageal neurostimulation, etc. However, refractory GERD is not an indication for surgery and surgical intervention is preferred only when patients do not respond adequately to medication.[42]

A recent systematic review conducted by El-Serag et al. reported that persistent breakthrough symptoms were observed in 30-60% of patients even after undergoing PPI treatment.[43] While PPIs effectively alleviate heartburn, regurgitation remains a prevalent complaint resistant to PPI therapy.[44] Additionally, some patients extend PPI usage beyond the recommended treatment duration, posing a risk of harm and significant financial implications.[8] In such scenarios, the introduction of alginate as an adjunctive therapy has demonstrated efficacy in reducing severe reflux symptoms, particularly in individuals with an inadequate response to PPIs, especially those with weak acid or non-acid reflux.[8] The SEA consensus attests alginates as a good adjunctive therapy for relief of GERD symptoms in patients with partial responsiveness to PPI therapy.[7] As per the world gastroenterology organization (WGO) global guidelines, antacids/alginates may be used in conditions where PPIs or H_2RAs are unavailable, or for prompt symptom relief in patients taking a PPI.[45] Combining antacids and alginates has been shown to be more effective in managing GERD symptoms compared to using antacids alone.[46]

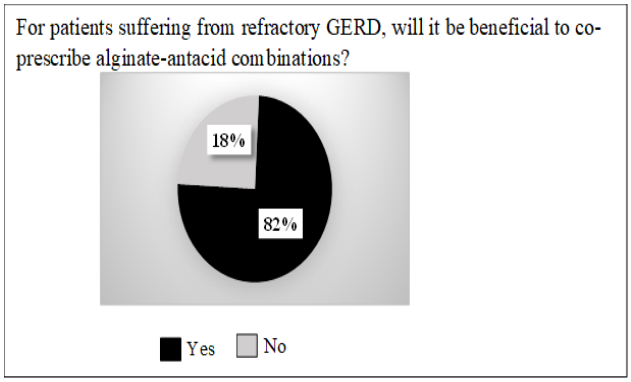

Figure 4: Co-prescribing alginate-antacid combinations may benefit patients with refractory GERD.

Expert opinion

In India, the prevalence of refractory GERD is <5%. In clinical practice, 60% of the panelists reported that 20-39% of their patients experience refractory GERD. Managing refractory GERD, addressing the psychological aspects using antianxiety and antidepressant medications is essential. Gradual deprescribing of PPIs is recommended, starting with dose reduction, and transitioning to on-demand use. The consensus is that PPIs should not be a long-term solution, and gradual deprescription or co-prescription with other acid neutralizers, such as alginate-antacid combinations, is preferable. Alginate primarily serves a role in symptom control for refractory GERD. Alginates can be used for a period of up to 6 weeks, thrice daily, as part of the management regimen alongside other acid suppressants like PPIs and H2RAs. The initial approach for refractory GERD involves combining alginate with a single dose of PPI before considering higher PPI doses. 82% of the panelists agreed that co-prescribing alginate-antacid

combinations would be advantageous for patients with refractory GERD (Figure 4).

MANAGEMENT OF GERD IN PREGNANCY

GERD stands out as the most prevalent gastrointestinal disorder in pregnancy, impacting nearly 40-50% of expectant women. Typically arising in the first trimester, GERD tends to persist throughout pregnancy, significantly affecting the overall quality of life for these women.[47] The development of GERD during pregnancy is commonly attributed to elevated progesterone levels, an enlarged uterus, and hormonal fluctuations inherent to pregnancy. Primary risk factors for experiencing GERD during pregnancy encompass pregnancy at an early age, a history of reflux either before or during gestation, as well as alcohol and tobacco use, medication use, and poor dietary habits. In pregnant women, endoscopy is not a standard diagnostic procedure for GERD unless there are severe symptoms such as severe hematemesis or dysphagia, whose frequency is less than 1%.[47] Lifestyle modifications is the initial strategy for the management of GERD along with avoidance of triggers. This conservative management approach includes consuming smaller meals, adopting a left side sleeping position or an elevated posture, avoiding fatty, oily, and acidic foods and beverages.[48] When considering pharmacological interventions for GERD during pregnancy, it is essential to take into account the FDA pregnancy categories.[48] For women experiencing severe GERD during pregnancy, prescribing a PPI other than Omeprazole is a suitable option, excluding the first trimester. H2RAs can also be avoided during the initial trimester. In the first trimester, alginates can be administered to pregnant individuals if H2RAs and PPIs are not considered suitable.[49]

Alginate-based treatments are deemed suitable for addressing pregnancy associated reflux conditions, given their non-systemic mode of action, minimal maternal absorption, and prompt onset of action.[50] A study conducted by Strugala et al assessed the safety and effectiveness of a raft-forming alginate reflux suppressor for managing pregnancy-related heartburn. Results indicated that approximately 67% of women experienced symptom relief within 10 minutes of taking the medication, and 91% reported relief within 20 minutes. Both mothers and fetuses were found to tolerate the therapy well, and it was deemed safe.[20]

Expert opinion

Alginate-antacids are considered suitable for managing hyperemesis gravidarum as they function as a physical barrier, preventing reflux. The duration of GERD treatment during pregnancy varies based on the severity of symptoms and the patient's profile. During the first trimester, treatment involves using alginate, Sucralfate, and antacids. In cases of increased severity, H2RA or PPI (except Omeprazole) may be prescribed for 4-6 weeks. Once symptoms subside, treatment can be discontinued. A similar approach is recommended for the third trimester. Experts caution against the long-term use of both PPIs and alginates in pregnant women. However, in instances of previously diagnosed Los Angeles (LA) Grade C or D reflux disease, a minimal dose of H2RA or PPI may be continued. Alginates are typically prescribed for on-demand use.

CONCLUSION

This review discusses the role of alginates in addressing various aspects of acid reflux. Alginates can be used as on demand or as a monotherapy in mild-to-moderate GERD. Use of PPIs should be rationalized and limited. Optimizing PPI therapy should be a priority, with appropriate deprescription, when required. Alginic acid-based formulations, primarily consisting of alginate and a bicarbonate salt, differ from traditional antacids in their mechanism of action and provide a quick relief and longer duration of action. Alginate monotherapy is a preferred choice for mild GERD symptoms. Alginates are a preferred option for acid reflux profiles such as postprandial reflux, nocturnal acid reflux, refractory GERD, and acid reflux in pregnant and lactating individuals and can be considered as a therapeutic option. Moreover, not all alginate-based raft-forming formulations are equivalent and physicochemical properties of the rafts impact their effectiveness in relieving GERD symptoms in clinical settings. Raft strength of alginate-antacid formulation is the most important property that has been preferred by the panelists while selecting a particular alginate-antacid for relief from acid reflux patients in these profiles.

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