

New algorithm for the treatment of gastro-oesophageal reflux disease

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SUMMARY

Background

Gastro-oesophageal reflux disease (GERD) is associated with a variety of typical and atypical symptoms. Patients often present in the first instance to a pharmacist or primary care physician and are subsequently referred to secondary care if initial management fails. Guidelines usually do not provide a clear guidance for all healthcare professionals with whom the patient may consult.

Aim

To update a 2002-treatment algorithm for GERD, making it more applicable to pharmacists as well as doctors.

Methods

A panel of international experts met to discuss the principles and practice of treating GERD.

Results

The updated algorithm for the management of GERD can be followed by pharmacists, for over-the-counter medications, primary care physicians, or secondary care gastroenterologists. The algorithm emphasizes the importance of life style changes to help control the triggers for heartburn and adjuvant therapies for rapid and adequate symptom relief. Proton pump inhibitors will remain a prominent treatment for GERD; however, the use of antacids and alginate-antacids (either alone or in combination with acid suppressants) is likely to increase.

Conclusion

The newly developed algorithm takes into account latest clinical practice experience, offering healthcare professionals clear and effective treatment options for the management of GERD.

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BACKGROUND

Gastro-oesophageal reflux disease (GERD), with its main symptoms of heartburn and regurgitation, is one of the most common conditions affecting the oesophagus; however, it has been appreciated that symptomatology in GERD patients is more complex and also extends to extra-oesophageal complaints and manifestations.¹ Estimates indicate that approximately 24% of the population will experience heartburn daily or more often, whilst 43% experience heartburn as often as once or twice a week.² Moreover, patients can typically experience chronic heartburn for periods ranging from less than 1 year (15%) to more than 10 years (29%).

From a therapeutic perspective, GERD is a disorder of both motility and oesophageal acid exposure, in as much that the signs, symptoms, and clinical conditions that characterize GERD result primarily from recurrent reflux of gastric contents into the oesophagus.³ These mechanisms include transient lower oesophageal sphincter relaxations and lower oesophageal sphincter pressure abnormalities, which can be caused by a variety of factors including hormonal and neural mediators, as well as medications, food, and patient lifestyle.⁴ Other factors that may contribute to the pathology of GERD include hiatal hernia, poor oesophageal clearance, and delayed gastric emptying.

Historically, acid reflux was believed to be the predominant cause of heartburn and other GERD symptoms, based on the induction of heartburn or chest pain during perfusion of the oesophagus with strongly acidic solutions.⁵ Current evidence, however, suggests that weakly acidic events in the oesophagus may also play a role in GERD symptom generation, particularly in patients taking proton pump inhibitors (PPIs), the main class of drugs prescribed for this condition.^{6–8} Although there is considerable evidence for the role of acid in the pathogenesis of GERD, studies that correlate oesophageal acid exposure to symptom events found at best a moderate temporal association between heartburn episodes and acid reflux events.^{5, 9}

The prevalence of GERD is the greatest in North America and Europe, with the highest rates seen in the USA (13–29%), Sweden (17%), UK (10%), and Spain (10%).¹⁰ Indeed, reflux disease is one of the most frequent disorders seen in primary care, as well as in secondary referral centres, and as such, has a high economic impact. PPIs dominate prescribing practices for dyspepsia and GERD but general practitioners are

under government pressure to change their prescribing habits through an economically driven perspective. As such, in the UK, guidelines from the National Institute for Clinical Excellence recommend that a healing dose of PPI is prescribed until symptoms are controlled; after this has been achieved, the dose of PPI is reduced incrementally (step down) until the lowest effective dose of PPI has been identified.¹¹ As reported by the experts at this consensus meeting, the generally recommended treatment in Europe for GERD symptoms at the primary care level is daily half-dose PPI, increasing to daily full dose PPI, and increasing to twice daily full dose PPI until symptoms are controlled. In those patients who prove refractory, the combination of a PPI plus antacids or alginate-antacids, histamine H₂-receptor antagonists (H₂RA) and lifestyle change may prove effective.¹² Antacids or alginate-antacids may be used to treat the symptoms of GERD in patients who choose to self-medicate, or to treat those symptoms that remain uncontrolled despite acid suppressant therapy.

To identify the best therapeutic options in GERD, a group of gastroenterological and pharmaceuticals experts met in Gstaad, Switzerland, to discuss and debate the principles and practices of treating GERD. The aim of these discussions was to update a consensus and opinion-based treatment algorithm developed at an earlier meeting in 2002.¹³

Several of the experts gave presentations concerning various aspects of GERD, focusing on current knowledge and clinical practice. This paper presents a summary of the discussions that enabled the panel to update the Gstaad Treatment Guidelines¹³ for reflux disorders by reaching a consensus on a practical treatment algorithm for GERD.

TREATMENT

Introduction

The lack of a clearly identified pathogenic process in GERD can confound diagnosis and treatment of this condition for both primary and secondary care physicians, as well as for patients who choose to self-medicate.

(i) A patient's first contact with a healthcare professional for GERD symptoms is typically during their visit to the pharmacy; it is widely agreed that this often only occurs after the patient has sought advice from friends and family. A meta-analysis covering the

period 1972 to 2005 by Tran *et al.*¹⁴ concluded that over-the-counter medications were effective in treating symptomatic GERD, and antacids and alginate-antacids were effective in the treatment of infrequent postprandial symptoms. At an OTC level of care, medical concerns include persistency of symptoms, the potential abuse of OTC PPI administration, and the potential of masking of malignancy by these agents.¹⁵

(ii) Primary care physicians (PCPs) are predominantly responsible for treating the 'typical' symptoms of GERD; however, PCPs are under pressure not to miss serious disease or misdiagnose cardiac or functional disorders as GERD, from the vast array of symptoms presented by the patient. The lack of accurate and reliable diagnostic tools, coupled with the overlap between symptoms of GERD and other abdominal or thoracic conditions, can make accurate diagnosis difficult.

(iii) Gastroenterologists in a secondary care setting treat patients who have been referred by PCPs, usually because the patient fails to respond to step-up PPIs or when the patient presents with a range of ambiguous symptoms. As a result, specialists are faced with the challenge of determining whether a GERD diagnosis is accurate for patients with symptoms that could be attributable to a number of underlying pathologies (Table 1).

The classical view of GERD focuses on acid reflux as the single most important component in the pathogenesis of this condition, with acid suppression being considered the predominant target for pharmacological therapy, with PPIs dominating the classical GERD treatment algorithm¹⁷ (Figure 1).

One of the current concerns in the diagnosis and treatment of GERD is the availability of new clinical data surrounding symptomatology and treatment. There is increasing evidence that indicates some patients not responding to PPIs. Indeed, many patients

with GERD are prescribed high dose or twice daily PPIs as a standard dose that is insufficiently effective; although, this lack of efficacy could in part be because of poor patient adherence and compliance.

It is also clear that the symptoms of GERD are not all entirely acid-related. Indeed, results from intraluminal impedance and pH monitoring studies show that a minority of patients with the so-called PPI-refractory GERD are suffering from ongoing acid (nadir pH < 4) reflux events, but that weakly acidic reflux events (nadir pH between 4 and 7) are now associated with symptom episodes.⁵⁻⁷ In addition, while ample evidence suggests that PPIs are the most effective agents for symptom control, oesophagitis healing, and stricture prevention in patients with GERD, in some patients, these drugs do not appear to normalize intra-oesophageal pH.¹⁸

A postprandial pocket of acid just below the gastro-oesophageal junction has recently been described,¹⁹ and in patients with reflux, this acid pocket shows greater proximal extension, and is longer (4–6 cm compared with 2 cm in healthy volunteers) perhaps because of shortening of the oesophageal longitudinal muscle. As this acid pocket can persist for up to 2 h postprandially and remains highly acidic compared with the body of the stomach, it is likely that gastric buffering from a meal creates a non-uniform environment with at least two acid layers; the lack of homogeneity of the stomach contents may explain persistent acidic gastro-oesophageal reflux after a meal²⁰ (Figure 2). It is postulated that antacids or alginate-antacids might raise the pH locally and so provide relief from this acid pocket, although at present, clinical data are unavailable to support this hypothesis.

The consensus opinion from the panel was that initial GERD treatment needs a symptom-based approach rather than a pathogenesis-based approach, where symptoms that respond to adequate acid suppressant

Table 1. Syndromes with symptomology associated with gastro-oesophageal reflux disease (according to the Montreal definition¹⁶)

Oesophageal syndromes	Extra-oesophageal syndromes established associations
Oesophageal symptomatic syndromes	Reflux cough syndrome
Typical reflux syndrome	Reflux asthma syndrome
Reflux/chest pain syndrome	Reflux laryngitis syndrome
	Reflux dental erosion syndrome
Syndromes with oesophageal injury	Proposed associations
Reflux oesophagitis	Pharyngitis
Reflux stricture	Sinusitis
Barrett's oesophagus	Recurrent otitis media
Oesophageal adenocarcinoma	Idiopathic pulmonary fibrosis

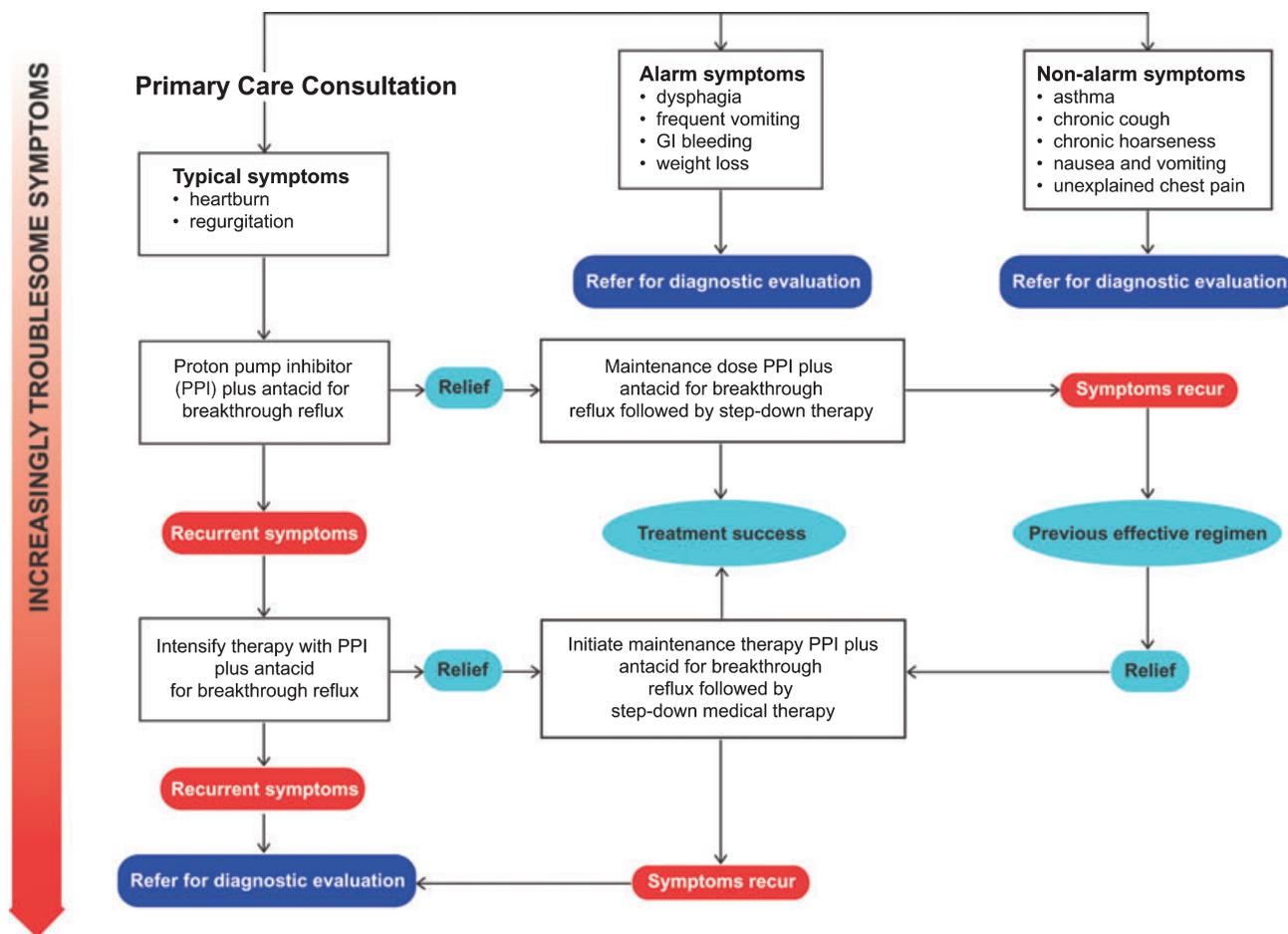


Figure 1. Reflux treatment guidelines for prescription medications (Adapted from Tytgat *et al. Aliment Pharmacol Ther* 2003;18: 291–301).

therapy confirm the role of acid reflux and symptoms nonresponsive to acid suppression confirm the role of other factors. Indeed, psychiatric comorbidity, somati-

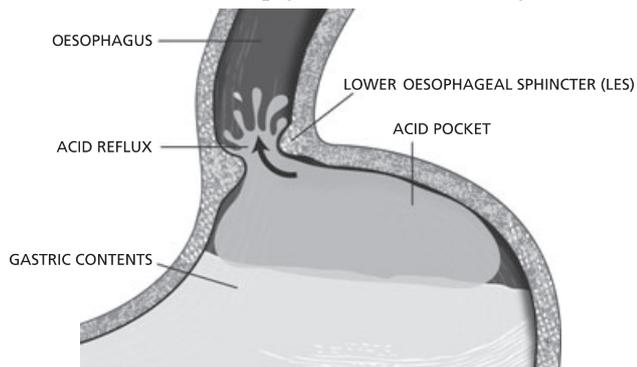


Figure 2. Postprandial acid pocket. This is a representation of the acid pocket; at this time the exact form and dimensions are to be determined.

zation, stress, anxiety, and insomnia are all factors that may influence GERD symptom generation, perception and response to therapy, and as such, may play a role in determining the most effective therapy. The panel also agreed that as the symptoms of GERD are not solely related to the secretion of acid, PPIs should not be considered as the only drugs of choice for GERD. Antacids or alginate-antacids may be an additional option for patients presenting at primary care with symptoms of reflux, or for patients with ongoing symptoms incompletely controlled with acid suppressants. However, further research is needed to determine the exact role for these agents in clinical practice.

Updated treatment algorithm. The updated treatment algorithm for the management of reflux disorders, developed during the 2006 expert panel meeting, is provided in Figure 3. This algorithm can be followed

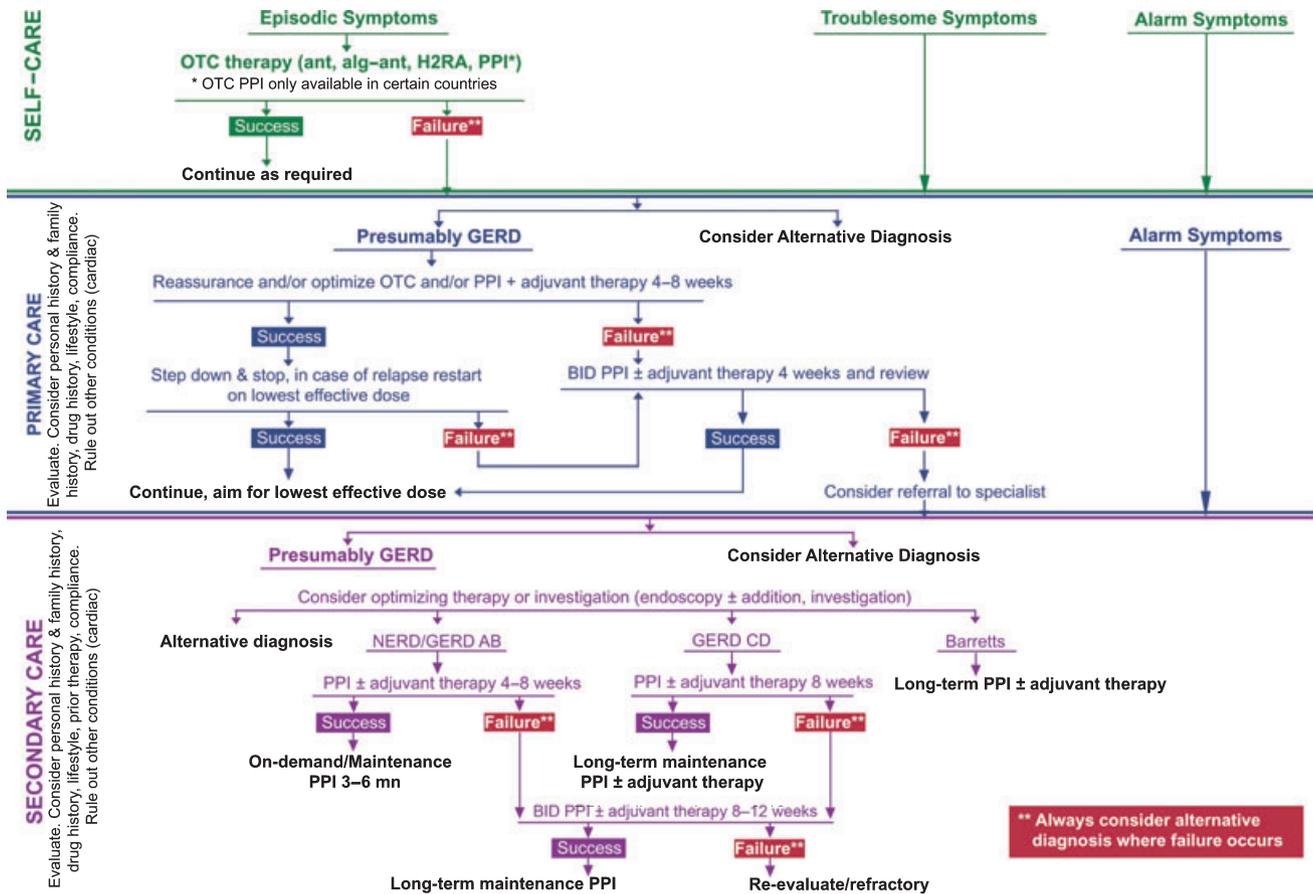


Figure 3. Updated treatment algorithm for the management of reflux disorders (2006). Definitions: *Adjuvant therapy*: corresponds to antacids or alginate-antacids (equivalent to 'rescue therapy'). *Alarm symptoms*: dysphagia, bleeding, anemia, weight loss, choking, chest pain, frequent vomiting. *Failure*: unresponsiveness to treatment, unsatisfactory symptom relief, too frequent use of treatment (over-the-counter, self-care level). *Intermittent*: defined as $\leq 1/\text{week}$. *Lowest effective dose*: lowest dose capable of providing symptom relief, which may range from no drug to single-dose proton pump inhibitor (PPI). *Step-down and stop*: reduction in PPI dose to half, then incrementally smaller doses until pharmacological treatment is terminated. *Troublesome symptoms*: defined as $\geq 2/\text{week}$.¹⁶

Additional notes: Short-term PPI self-medication is accepted, although it is noted that this will not provide immediate symptom relief, based upon molecular mode of action. The inclusion of adjuvant therapy, in combination with PPIs, is based upon clinical experience and data from meta-analyses. It is recognized that, at this time, there is no evidence for judging one pharmacological agent to be superior to another in terms of speed of symptom relief, and further data are required to support this algorithm. The panel does, however, believe that antacids or alginate-antacids offer symptom relief more rapidly than alternative treatments and can be used in combination with acid suppressants to treat remaining or breakthrough symptoms.

by patients and pharmacists when choosing OTC medications, PCPs and gastroenterologists in a secondary care setting.

Overview

The algorithm is separated into three distinct therapeutic levels (self-care, primary care, and secondary care), with clear recommendations being provided at each level of care.

The vast majority of patients with reflux symptoms can be controlled at the self-care and primary care levels, and as such guidance needs to be provided on the treatment of mild to severe symptoms of GERD.

Approaches to reflux should focus on best clinical practice, where treatment of symptoms is the main priority. The PCP also needs to use a symptom-based approach to match patients with the best treatments for their particular manifestation of GERD and lifestyle. Antacids and alginate-antacids should be considered at

the self and primary care level, as these agents can be used for intermittent and rapid symptom relief.

The algorithm emphasizes the importance of lifestyle factors, although these are not well supported by clinical data now. Lifestyle factors include meal size and timing, as well as not lying down after a meal or lying down where the head is in a non-elevated position, not smoking, not consuming alcohol, and not eating heavily spiced or fatty foods.²¹ From clinical experience, these factors appear to be triggers for GERD and heartburn; however, if monitored, can minimize the occurrence of sporadic or breakthrough symptoms. In addition, by providing advice on these lifestyle measures, pharmacists and physicians may be able to help ease the patient's milder symptoms of heartburn. This advice needs to be disseminated to patients and all those involved in their treatment.

In all levels of the algorithm, symptom definition is critical. It is also crucial that at every stage, cardiac disorders are eliminated as an underlying pathology for the symptoms; equally, drug-related symptoms and lifestyle factors also warrant significant consideration to ensure the most suitable treatment is offered to the patient. A careful history and physical evaluation is essential, and consideration given as to whether the symptoms warrant an alternative diagnosis. Any alarm symptoms should be immediately referred for specialist investigation.

Self-care

The panel largely agreed that low-dosed PPIs should remain an available treatment option for GERD patients at the self-care level. Despite their restrictions, particularly a somewhat limited therapeutic benefit from intermittent use, low-dosed PPIs are readily available in some countries, including the United States, and are a viable option for short-term GERD symptom relief. The panel also agreed that the most important factors in determining the appropriate OTC therapy should be speed of action and onset of symptom relief. Antacids or alginate-antacids offer the most rapid symptom relief and can be taken 'as required'.

At the self-care level, guidance to the pharmacist is equally as important as guidance to the patient. If patients have persistent symptoms or symptoms occurring frequently (≥ 2 times per week), the pharmacist should recommend that the patient seeks further medical advice.

Patients presenting with alarm symptoms, including dysphagia, bleeding, weight loss, choking, chest pain or frequent vomiting, are strongly advised to contact their PCP for referral to specialist care.

In addition, effective public health campaigns are needed to disseminate the key messages surrounding self-care, from education about mild symptoms to warning or alarm symptoms and advice on treatment strategies.

Primary care

As a general rule, PCPs see reflux symptoms in all guises and are responsible for assessing and treating the problem on a clinical basis. As a result, PCPs can assume a wide scope of treatment options, which embrace a symptom-based approach, normally focusing on the predominant symptom. It was noted by the panel that the majority of GERD cases can be controlled without referral to secondary care.

At the primary care level, PPI or a combination of alginate-antacid and acid suppressive therapy can be administered at the discretion of the physician, as combination therapy, which may potentially be more beneficial than acid suppressive therapy alone. Similarly, patients who fail full-dose PPIs, plus/minus adjuvant therapies, may benefit from step-up therapy to twice daily PPIs. If the patient fails to respond to this increased dose, an alternative diagnosis should be considered and possibly referral to secondary care.

For patients who are successful on single-dose PPIs, the panel agreed that a step-down approach is appropriate so that the dose is lowered incrementally until treatment is stopped. In the case of symptom recurrence, the physician is advised to resume treatment, aiming for the lowest effective maintenance dose.

Secondary care

Specialists at the secondary care level are responsible for dealing with more complex cases, e.g. patients who are partially or completely unresponsive to treatment. In this role, the specialist needs to confirm the diagnosis, determine a prognosis and identify suitable long-term treatment strategy for the patient.

A full patient evaluation is essential, and it is mandatory that consideration is given as to whether the symptoms merit an alternative diagnosis, or whether further investigation is needed because of the presence of alarm symptoms.

Endoscopic examination was included in the new algorithm as an option for further therapy (or as method of investigation), because of differing clinical practice in the various countries represented at this expert panel meeting.

The guidelines for treatment were further subdivided based upon the severity of mucosal damage: non-erosive reflux disease/GERD AB, GERD CD and Barrett's oesophagus. If the patient fails to respond to treatment, double-dose PPIs are to be prescribed, and if these fail, then alternative diagnoses should be sought. The role of pH monitoring off PPI vs. pH/impedance monitoring on PPI in these patients needs to be carefully studied in management trials. Treatment options for true refractory GERD include anti-reflux surgery and potentially, based on few observations, addition of baclofen in selected cases.²²

CONCLUSIONS

The revised algorithm (Figure 3) reflects current practices and, to maximize patient satisfaction and disease management, also includes advice on the optimum management of symptoms divided into three levels of care (self-care, primary care and secondary care).

At the self-care level (and in addition to PPI treatments), a prominent role was given to the widely available OTC medications such as antacids, alginate-antacids, H2RA. Antacids or alginate-antacids, as adjuvant therapies, were also given a more prominent role in all levels of GERD treatment, both independently and in combination with acid suppressive therapies. This was because antacids and alginate-antacids have the ability to provide a rapid and adequate relief from symptoms of GERD. Additionally, bile and pepsin erosion, via the formation of a raft-like structure in the acid pocket (their mode of action),²³ can be reduced by alginate-antacids treatment.

At the primary care level, it was recognized that patients frequently present with undifferentiated symptoms, whilst managing these on a clinical basis can be challenging for the physician. For some patients not responding to initial measures and acid suppression at standard dose, increasing the level of acid suppression may be beneficial. However, the need to consider alternative diagnoses was important, together with the option of referral to secondary care.

At secondary level, endoscopic examination of unresponsive patients was redefined as optional, to reflect differing practices and medical guidelines between countries.

Much emphasis was given to the re-evaluation of patients at all stages throughout their treatment, including an assessment of factors such as lifestyle, family history, and compliance.

In conclusion, the newly developed algorithm takes into account latest clinical practice and experience, so it is hoped, offers healthcare professionals clear and effective treatment options and guidelines for the management of GERD.

Further research is, however, needed to identify the relationship between the symptoms of GERD, acid production and disease pathology as this will allow additional refinement of this algorithm.

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