Reflux Symptoms: Functional and Structural Diseases and the Approach from the GI Specialist

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Abstract

The GI specialist has an important role to play in the long-term management of gastroesophageal reflux disease (GERD) patients to secure a proper diagnosis and the selection of best possible therapeutic strategy. Through intensified information and education, the implementation of national and international guidelines can be more effectively processed, whereupon a significant improvement in cost-effectiveness of the current management will be fostered. Regarding the more specific group of GERD patients, as represented by the so-called PPI-refractory patients, data have now emerged to guide us into the future. Noteworthy is that the majority of the alleged PPI-refractory GERD patients do not, after careful investigations, have GERD. Based on recently published RCT data, a clinically highly relevant difference in treatment success was noted in favor of laparoscopic antireflux surgery as compared to a variety of medical treatment alternatives. Likewise, it can be concluded that it seems as if the latter can only offer a limited effect. Whenever a corresponding powerful clinical difference in therapeutic out-

come between different strategies and treatment alternatives is detected, this will have a huge impact on treatment algorithms and clinical management.

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Introduction

Gastroesophageal reflux disease (GERD) manifests itself in the form of specific esophageal erosive lesions and a wide range of symptoms that can be subdivided into typical, atypical, and extraesophageal [1]. Although GERD symptoms are often mild and not life threatening, GERD has a great impact on the quality of life of patients [2, 3]. Acid suppression with proton pump inhibitors (PPIs) is the mainstay of therapy for GERD which normalizes quality of life in these patients. In cases where patients present with atypical symptoms (e.g., supraesophageal symptoms) and lack mucosal abnormalities at endoscopy, these conditions add to the complexity of reaching a robust diagnosis. Often patients have been prescribed PPIs before being referred to gastrointestinal specialists. In such situation, it can sometimes be difficult to know whether the presenting symptoms are indeed due to reflux. Although there is no consensus about defi-

Fig. 1. a Annual incidence and prevalence/100 inhabitants of PPI use. Modified after [19, 20]. **b** Number of prescriptions of PPIs in Sweden during the years 2006–2019. In these figures are not included the OTC deliveries of PPI (by courtesy of the Swedish National Board of Health and Welfare data base 2020-11-10). PPI, proton pump inhibitor; LARS, laparoscopic antireflux surgery.

nition of failure-refractoriness, 30–40% of patients with GERD do not achieve adequate symptom relief after a 4-week course of a single dose of PPI [4, 5]. Noteworthy is that erosive esophageal reflux disease is more difficult to treat with H2RA compared with PPIs, and patients with esophagitis tend to have improved symptomatic relief with PPIs compared with patients with nonerosive esophageal reflux disease. Maintenance PPI therapy to prevent symptom relapse is often required and the lowest effective PPI dose is recommended in erosive reflux disease. In contrast, patients with NERD carry the potential to be managed successfully with on-demand PPI. The feasibility of step-down therapy in patients with GERD has

been documented and more than half of patients in the step-down group were asymptomatic on either non-PPI therapy or no therapy at all, when assessed after a year [6]. Given the high cost associated with indefinite PPI use, attempts should be made to treat patients with the least expensive yet effective medication.

Inappropriate Use-Prescription of PPI

There is no doubt that PPI therapy has revolutionized our approach to management of acid-related GI conditions, and the results have been excellent and significant-

Table 1. Main causes behind inappropriate use of PPI therapy (modified after [12])

1. Continuation of PPIs prescribed inappropriately upon hospital discharge
2. Absence of regular doctors' re-evaluation of their patients allegedly prescribed chronic PPI therapy
3. Wrong diagnosis of the acid-related disorder
4. Overtreatment of functional dyspepsia
5. NSAID/ASA/COXIB use in patients <65 years or without other risk factors
6. Improper prescription of PPIs during the hospital stay
7. Steroids intake alone
8. SSRIs intake alone
9. Low molecular heparin or warfarin alone in patients without risk factors
10. Ticlopidine or clopidogrel alone in patients without risk factors
11. Stress ulcer prophylaxis in non-ICU patients
12. Patients with chronic liver disease and portal hypertension

In the table are stratified the respective causes in order, based on their assumed clinical importance – impact. PPI, proton pump inhibitor.

ly superior to those achieved with H₂RAs. Nevertheless, PPI use continues to grow every year (Fig. 1a, b) in all countries where the topic has been studied, and this must bring to our attention the role of PPI misuse in both hospital and primary care settings. In fact, it has been calculated that >50% of PPIs are prescribed inappropriately in medical wards and in general practitioners' practice [7–10], and these rates are worrying because they suggest that PPI use is governed by indications different from those recommended by expert consensus statements [11].

Evaluation of the corresponding PPI practice during varying follow-up periods has shown that significant changes in the PPI prescription do not occur over time (Fig. 1b). In the corresponding analyses, no difference is seen in this overprescription pattern between academic and nonacademic health-care institutions [12]. Concerning all these studies, however, there is a methodological problem in that the majority of the studies are retrospective. Interestingly, a significant factor behind the inappropriate in-hospital continuation of PPI treatment is that the patient was already on PPI at the time of hospitalization and at that time point a critical reflection, regarding the continued need for a PPI prescription, was not done. To this fact must be added that hospital doctors often continue to prescribe these drugs in the belief that the previous prescription was correct and that the initiated treatment must be continued [13, 14]. Lack of adher-

ence to national-international guidelines and scientifically based indications for treatment constitutes a clear reason for this continued overprescribing of PPIs (Table 1). In primary care, PPI prescribing often just continues, after the patients have been discharged from hospital. In outpatient care, functional dyspepsia is a clinical area with a high risk of PPI overprescription [15]. It is well known that in primary care these drugs are frequently prescribed to these patients indefinitely without any periodic re-evaluation to reduce the dose or to cease treatment [12].

Discontinuation of PPI Therapy

For patients who are prescribed PPI therapy on unclear-inaccurate indications or symptoms, the discontinuation of these drugs must be attempted. However, the sudden withdrawal of PPIs may cause a marked rise in gastric acid secretion, a phenomenon known as “rebound gastric acid hypersecretion.” As a consequence, this may induce or aggravate upper GI symptoms. Reimer et al. [16] originally demonstrated that up to 40% of healthy individuals, who discontinued PPIs after 8 weeks of treatment, reported dyspepsia during the following 4 weeks. Niklasson et al. [17] showed that symptoms on PPI discontinuation were significantly correlated with the degree of PPI-induced hypergastrinemia. In a study containing 78 patients not having a clear indication for PPI use, nearly two-thirds developed upper GI symptoms within 6 months of PPI withdrawal. As much as 40% of them had endoscopic findings consistent with their symptoms, that is, mostly mild esophagitis [18]. Obviously, it is important to avoid an abrupt withdrawal of PPIs, particularly in chronic users, and adopt a strategy aimed at reducing-avoiding the phenomenon of “rebound acid hypersecretion.” PPI withdrawal can be achieved by stepping down to a lower dose or to an intermittent/on-demand regimen or by replacing PPIs with a less potent acid inhibitor, such as H₂ receptor antagonists [21].

PPI-Refractory GERD

With increasing experience of PPI treatment of GERD, a consistent clinical picture has emerged meaning that at the very most, 75% of these patients achieve a satisfactory control of the reflux symptoms on PPI therapy [4, 5]. In the remaining group of patients, the physician has to consider a number of factors that may explain the lack of PPI

Table 2. Factors that may explain the lack of PPI effect in GERD patients

Abnormal and continued acid reflux persists despite PPI treatment
The patient does not take his medicine as prescribed
There is a hypersensitivity in the epithelium of the esophagus, which means that symptoms occur despite the fact that only “normal” amounts of acidic material is regurgitated into the distal esophagus
Heartburn or similar symptoms are caused by other than GERD (e.g., achalasia and eosinophilic esophagitis)
Heartburn is part of a dysfunctional condition (i.e., does not occur due to GERD or any other histopathologically identifiable, muscular, or other structural abnormality)
PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease.

Table 3. Management of PPI therapy failure in chronic GERD

a. Endoscopy + biopsy
b. Outpatient 24-h pH measurement
c. Preferably simultaneous, ambulatory 24-h impedance and 24-h pH measurement
d. The relationship between symptoms and objective occurrence of different types of gastroesophageal reflux
The following examinations should ideally be performed both during and after discontinuation of PPI treatment. PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; SAP, symptom association probability; SI, symptom index.

effect in GERD patients, and those are summarized in Table 2. To avoid that the PPI is given based on an incorrect indication, and to inaccurately manage these PPI-refractory GERD patients, the following pragmatic management options can be recommended: (1) be always prepared to question the diagnosis; (2) check that the patient is actually taking the prescribed PPI; (3) adjust PPI intake in relation to food intake (before breakfast and other food intake); (4) if needed, try another type of PPI; (5) do not hesitate to double the PPI dose (twice daily); (6) in a few cases, consider to add H₂ blockers (and/or alginate – e.g., Gaviscon) at bedtime if nocturnal symptoms; (7) at a later stage, consider more complex pharmacological treatment (see below); and (8) above all, do not forget to test for *Helicobacter pylori* and eradicate if the bacterium is

present, not the least if continued long-term treatment with PPI is planned (otherwise increased risk of gastric mucosal dysplasia).

In the event that modified dosing of PPI continues to provide insufficient symptom relief, drugs may be given aiming at increasing the tone of the lower esophageal sphincter and improving the esophageal muscular cleansing effect of the refluxed material. Such drugs are baclofen or other neuromodulators (desipramine). Tricyclic antidepressants have also been tried with the aim of suppressing visceral hypersensitivity. Baclofen and other neuromodulators often have some troublesome side effects, and studies of their effect in PPI-failing GERD patients are rather limited, so these drugs should be prescribed only by specialists.

The further investigation of GERD patients with PPI resistance should include the examinations listed in the Table 3 [4, 5].

Today, these functional tests are performed in specialist laboratories in the form of high-resolution esophageal manometry, and multichannel intraluminal impedance and pH measurement. The advantage of impedance measurement is that this technology allows a separation of acid reflux from pure alkaline reflux as well as from regurgitation of air alone. In connection with such ambulatory tests, it is important that the relationship between the different types of reflux events and any symptoms is registered. For more detailed diagnostic interpretation of these outcomes, see Table 4.

The Role of Surgery in PPI-Refractory GERD

There are a number of well-designed randomized clinical trials where PPI therapy has been compared to anti-reflux surgery in chronic GERD patients. Most of these demonstrate a certain superiority of the long-term surgical strategy when it comes to reflux control [22–25]. It should, however, be kept in mind that an important inclusion criterion in these studies has often been that patients have already responded well to PPI treatment in the past (i.e., we are not talking about PPI-refractory GERD). Regarding traditional health-economic comparisons between the medical and the surgical treatment strategy, such studies lag behind, as the cost profiles vary both over time and also greatly between different countries and health-care systems. However, it is important that these evidence-based facts are communicated to patients with chronic GERD (for details see Table 5), who for various reasons are interested in discussing alternative long-term

Table 4. Definitions of gastroesophageal reflux subtypes according to endoscopy and pH-impedance monitoring and Rome III definitions

1. Erosive reflux disease: patients with mucosal breaks at endoscopy
2. Nonerosive reflux disease: patients without any mucosal break at endoscopy and abnormal esophageal acid exposure at 24-h esophageal pH monitoring
3. Hypersensitive esophagus: patients without any mucosal break at endoscopy, normal esophageal acid exposure, and positive symptom-reflux association analysis (SI >50%; SAP >95%)
4. Functional heartburn: patients with heartburn refractory to PPIs, without any mucosal break at endoscopy, normal esophageal acid exposure, and negative symptom reflux association analysis (SI <50%; SAP <95%) at 24-h esophageal pH monitoring
5. Weakly acidic reflux: gastroesophageal reflux episode detected by esophageal impedance and associated with an esophageal pH between 4 and 7
6. Weakly alkaline reflux: gastroesophageal reflux episode detected by esophageal impedance and associated with an esophageal pH above 7
7. Nonacid reflux: usually refers to all reflux episodes detected by esophageal impedance without any pH drop below 4 (include weakly acidic and weakly alkaline reflux)
PPI, proton pump inhibitor; SAP, symptom association probability; SI, symptom index (modified after [4, 5]).

treatment strategies rather than simply continuing a life-long PPI treatment [26]. In addition to this group of chronic GERD patients, those with predominant volume reflux symptoms (perhaps with aspiration tendency) should be offered a referral for surgical consultation. On the other hand, in the case of GERD patients with possible so-called extraesophageal symptoms (asthma, laryngitis, bronchitis, and noncardiac chest pain), it is still doubtful whether surgical treatment effectively controls other than the classic GERD symptoms.

A traditional indication for surgical treatment is represented by GERD patients with so-called “therapy failure” on modern PPI treatment. This indication is well known from all textbooks, but the hard evidence is still lacking how effective funduplications are in this rather complicated group of patients. Until recently, no controlled randomized trial data provided clear therapeutic guidance. Spechler and colleagues [27] from various centers in the United States published a study that addressed the question of whether antireflux surgery was superior to adopted medical treatment in patients with well-diagnosed PPI-resistant heartburn. All patients, who were referred to VA gastroenterology clinics, for heartburn resistant to traditional PPI treatment, were examined according to the principles previously described to actually document that GERD disease was the cause of the current problems. A total of 366 patients were included for screening and minority of these patients were found to have GERD, despite long-term PPI treatment. The remaining 78 patients underwent randomization and after 12

Table 5. Indications for antireflux surgery in chronic GERD patients considered fit for a surgical procedure

Need for continuous medical therapy (PPI dependency)
In complete clinical response to PPI
Well-documented PPI refractoriness
Volume reflux
Patients’ own preferences!
Prognostic factors
✓ Male gender
✓ Symptoms relieved by PPI’s
✓ Volume reflux
✓ Positive 24-h pH with typical symptoms, that is, high SAP or SI
✓ Hiatus hernia
✓ Type of fundoplication (advantage with a posterior partial fundoplication)
✓ Operation carried out at an expert center

The lower section of the table specifies the predictive factors for a successful operation. PPI, proton pump inhibitor; GERD, gastroesophageal reflux disease; SAP, symptom association probability; SI, symptom index.

months of follow-up, the results were convincingly in favor of the surgical strategy (Fig. 2). In fact, it can be said that continued medical treatment seems to be rather ineffective and in some cases burdened by significant side effects.

Fig. 2. The outcome of medical or surgical treatment of PPI-refractory heartburn. Treatment success at 12 months defined as $\geq 50\%$ improvement from the baseline GERD-HRQL score. LARS, laparoscopic antireflux surgery (Nissen). Modified after [27].

Barrett's Esophagus

Due to the progressive increase in the incidence of adenocarcinoma of the esophagus (ACE) and gastroesophageal junction, gastroenterologists have focused on the identification and surveillance of patients at risk of these lethal tumors. Barrett's esophagus (BE) is the well-recognized precursor lesion of ACE through the sequence columnar metaplasia-dysplasia-adenocarcinoma. The diagnosis of BE leans completely on the endoscopic identification and to that the early detection and treatment of dysplastic lesions and early ACE. If management is carried out according to those principles, a great chance is offered the BE subjects to prevent the development of invasive cancer. However, the majority of ACE cases are still diagnosed outside the surveillance programs, bringing into question if the population at risk of ACE is correctly identified and managed [28–30]. BE should be diagnosed when there are extensions of columnar epithelium into the distal esophagus extending 1 cm or more proximal to the gastroesophageal junction (tongues or circular) with histologic confirmation of specialized intestinal metaplasia. Hereby, the endoscopist uses high-definition white-light endoscope. The Prague classifica-

tion is mandatory to use [31] which utilizes important landmarks to determine the total length and the extent of circumferential columnar mucosa. Any endoscopic abnormalities should be documented using the Paris classification [32]. Many guidelines recommend the use of Seattle protocol for biopsy in order to increase the yield in dysplasia detection [30]. Most guidelines recommend 3–5 years of endoscopic surveillance for patients with nondysplastic BE. Given these important management implications, the diagnosis of any degree of dysplasia (indefinite, low and high grades) in BE requires confirmation by a second and expert gastrointestinal pathologist [28–30].

The addition of p53 immunostaining to the histopathological assessment may improve the diagnostic reproducibility of dysplasia. Regarding low-grade dysplasia without visible lesions, repeating a high-quality endoscopy is recommended. If low-grade dysplasia persists at the second endoscopy, ablation therapy or endoscopic surveillance should be proposed. Concerning high-grade dysplasia (HGD) without visible lesion, most guidelines recommend repeating high-quality endoscopy to look for abnormalities, and if no visible lesions are detected, ablation therapy is proposed. In the case where no lesion is found, at repeat endoscopy within 3 months, and these biopsies confirm the presence of HGD, endoscopic ablation is recommended, preferably with radio frequency ablation. All visible lesions should be endoscopically resected (irrespective of nondysplastic or dysplastic BE), aiming for free margins, and the remaining dysplastic columnar-lined mucosa shall be ablated.

Chemoprevention is an attractive strategy for BE with the potential to prevent ACE from occurring. There are a number of promising candidates that may decrease the risk for progression to esophageal adenocarcinoma, all based on observational studies [33]. It can, however, currently be concluded that there is insufficient evidence to recommend metformin or hormone replacement therapy for chemoprevention in BE. There is also insufficient evidence to recommend statins to decrease the risk for esophageal adenocarcinoma, but patients with BE should be carefully evaluated to assess if there is a cardiovascular indication for similar drugs. Twice-daily proton pump inhibitor therapy combined with aspirin shows the most promise in preventing neoplastic progression in BE and seems to decrease all-cause mortality [34] and affect the risk for ACE and HGD development as well.

Comments

Obviously, the GI specialist has an important role to play in the long-term management of GERD patients (with or without BE), to secure a proper diagnosis and the selection of best possible therapeutic strategy. Noteworthy is that PPI use continues to grow every year in all countries where the topic has been studied, and this must bring to our attention the role of PPI misuse in both hospital and primary care settings. In fact, it has been calculated that >50% of PPIs are prescribed inappropriately in medical wards and in general practitioners' practice. Through intensified information and education, the implementation of guidelines can be more effectively processed, whereupon a significant improvement in cost-effectiveness of the current management will be fostered. Regarding the more specific group of GERD patients, as represented by the so-called PPI refractoriness, data have now emerged to guide us into the future. The majority of the alleged PPI-refractory GERD patients do not, after careful and generally accepted investigations, have GERD. In many studies only about 1/3 of these patients will eventually meet the pre-established criteria for PPI-resistant GERD heartburn. An uncritical approach to and lack of rigor in the investigation of these presumed GERD patients pave the way for a situation where many patients receive continued ineffective and completely misdirected treatment [4, 5]. Given that these investigations are completed, it can be assumed that a relatively limited number of GERD patients, who actually fail on PPI treatment, will eventually need to be referred for a decision on, for example, surgical treatment. What we now know, based on the study by Spechler and co-workers [27], is that already the year after the randomization, a dramatic difference in

treatment success was noted in favor of laparoscopic Nissen (360°) fundoplication. Regarding the effect of the other 2 medical treatment alternatives, it could be stated that these seem to have only a limited effect with no difference between the 2 different medical treatment alternatives other than that the side-effect profile which was significant in those allocated to more complex multipharmacies. Whenever a corresponding powerful clinical difference in therapeutic outcome between different strategies-treatment alternatives is detected, this will ultimately have a huge impact on treatment algorithms and clinical therapeutic management.

Statement of Ethics

All research referred to in the text has been conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The current manuscript is exempt from Ethics Committee approval due to its review-meeting report character.

Conflict of Interest Statement

No conflicts of interest to be declared.

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