FOCUS ON GASTROESOPHAGEAL REFLUX (GER) AND LARYNGOPHARYNGEAL REFLUX (LPR): NEW PRAGMATIC INSIGHTS IN CLINICAL PRACTICE

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Introduction:

Gastroesophageal reflux (GER) is a common disease usually limited to the oesophagus. Laryngopharyngeal reflux (LPR) is an inflammatory reaction of the mucosa of pharynx, larynx, and other associated upper respiratory organs, caused by a reflux of stomach contents outside the oesophagus. LPR is considered to be a relatively new clinical entity with a vast number of clinical manifestations which are treated sometimes empirically and without a correct diagnosis. However, there is disagreement between specialists about its definition and management: gastroenterologists consider LPR to be a substantially rare manifestation of gastroesophageal reflux disease (GERD), whereas otolaryngologists believe that LPR is an independent, but common in their practice, disorder. Patients suffering from LPR firstly consult their general practitioners, but a multidisciplinary approach may be fruitful to define a unified strategy based on specific medications and behavioural changes. The present Supplement would review the topic, considering LPR and GER characteristics, pathophysiology, diagnostic work-up, and new therapeutic strategies also comparing different specialist points of view and patient populations. In particular, new insights derive from an interesting gel compound, containing magnesium alginate and E-Gastryal® (hyaluronic acid, hydrolysed keratin, Tara gum, and Xantana gum). In particular, two very large Italian surveys were conducted in real-world setting, such as outpatient clinics. The most relevant outcomes are presented and discussed in the current Issue.

Actually, laryngopharyngeal reflux (LPR) is considered an extraesophageal manifestation of the gastroesophageal reflux disease (GERD). Both GERD and its extraesophageal manifestation are very common in clinical practice. Both disorders have a relevant burden for the society: about this topic most of pharmaco-economic studies were conducted in the United States. In population-based studies, 19.8% of North Americans complain of typical symptoms of GERD (heartburn and regurgitation) at least weekly (1). Also in the late 1990s, GERD accounted for $9.3 to $12.1 billion in direct annual healthcare costs in the United States, higher than any other digestive disease. As a result, acid-suppressive agents were the leading pharmaceutical expenditure in the United States. The prevalence of GERD in the primary care setting becomes even more evident when one considers that, in the United States, 4.6 million office encounters annually are primarily for GERD, whereas 9.1 million encounters include GERD in the top 3 diagnoses for the encounter. GERD is also the most frequently first-listed gastrointestinal diagnosis in ambulatory care visits (2, 3) Extraesophageal manifestations of reflux, including LPR, asthma, and chronic cough, have been estimated to cost $5438 per patient in direct medical expenses in the first year after presentation and $13,700 for 5 years.

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Estimates of the economic burden of extraesophageal reflux have shown that expenditures for extraesophageal manifestations of reflux could surpass $50 billion, 86% of which could be attributable to pharmaceutical costs (2,3) In addition, the National Health Care Survey carried out by the Center for Disease Control and Prevention has demonstrated that the chief complaint for primary care patient visits was cough in 6.1%, throat symptoms in 4%, and asthma in 2.8% (4). Within these visits for cough, asthma, and throat symptoms are contained the hidden prevalence of extraesophageal manifestations of GERD, which to date have not been adequately addressed from a medical or surgical perspective due to their perceived obscurity. Therefore, gastric reflux represents a very important medical issue that deserves adequate attention.

From a pathophysiological point of view, gastric reflux includes different mechanisms, such as the provocation and perception of reflux. The transient lower oesophageal sphincter relaxations (TLESR), hiatus hernia, acid pocket, visceral hypersensitivity, and obesity represent important causes of gastric reflux. Impaired oesophageal, and extraesophageal, mucosal integrity, poor oesophageal clearance, and delayed gastric emptying could be associated with GERD development. In addition, another pathogenic factor is a neural reflex sustained by acid exposure: the so-called Reflex-Reflux (5).

Distinguishing whether cough, LPR, and asthma are caused by GERD remains challenging for both the primary care physician and the specialist. This distinction is important because treatment of GERD with the intent of improving or curing extraesophageal manifestation can be ineffective. To review the current literature on extraesophageal manifestations of reflux should assist in clinical decision making.

The Montreal Classification provides the most recent consensus definition of GERD. It defines GERD as heartburn symptoms or complications resulting from the reflux of gastric contents into the oesophagus, up to the oral cavity, and lungs (5). GERD is further classified into two subgroups. The first subgroup is GERD with heartburn symptoms but without endoscopic evidence of mucosal erosions (Non-Erosive Reflux Disease or NERD). The second sub-group is GERD with heartburn symptoms accompanied by objective evidence of erosions, ulcers, and inflammation (Erosive Reflux Disease or ERD) (6). Functional heartburn also falls under endoscopic negative disease. However, it is important to note that it is a distinct entity from NERD. NERD is defined as typical reflux symptoms without evidence of reflux disease in endoscopy but abnormal acid exposure on the impedance-pH monitoring and is responsive to PPI (7,8). Functional heartburn on the other hand, as defined by Rome IV classification, is a retrosternal burning discomfort or pain refractory to anti-secretory therapy without presence of GERD, histopathologic abnormality, motility disorder or structural abnormality for at least three months with symptoms onset at least six months prior to the diagnosis (5).

As just defined, stomach content may also reflux outside of the oesophagus into respiratory organs, such as extraesophageal reflux, including LPR. LPR is most commonly manifested as laryngeal symptoms such as coughing, hoarseness, dysphagia, globus, and sore throat, but there can be signs also of nose, sinus, ear, and eye involvement (9). Epidemiological studies have shown that the prevalence of this LPR may be extremely high, that it has certain characteristics of an outbreak and that it is one of the most common causes of patient visits to their family medicine physicians, but also to otolaryngologists, gastroenterologists, paediatricians, pulmonologists, allergists, and psychiatrists (1,10-13). Today it has been proven that gastroesophageal reflux is not the only cause of LPR. LPR is a multifactorial syndrome with a vast clinical representation, during the disease and with complications, so it requires and deserves a multidisciplinary approach. Based on newly discovered findings about the specific pathogenesis of the disease, LPR may be considered a new clinical entity (11-13).

As once pointed out, GERD is caused by the lower oesophageal sphincter dysfunction and the dysfunction of the stomach emptying mechanism. Oesophageal mucosa has protective mechanisms against aggressive factors of the stomach content (mucosal barrier) and it remains intact when a

physiological reflux occurs, which normally happens at night. However, laryngeal and pharyngeal mucosa do not possess the oesophageal protective mechanisms, so acid and peptic activity of the stomach content quickly leads to mucosal lesions. Notably, laryngopharyngeal reflux occurs most commonly during the day as a result of the upper oesophageal sphincter dysfunction. This aspect is intriguing as typical GERD symptoms usually occur in supine position and overnight. However, acidity of the stomach content is not the only cause of LPR. Pepsin with its proteolytic effects can be the determining factor. Other possible etiological factors are pancreatic proteolytic enzymes, bile salts, and bacteria (1, 13, 14). Extraesophageal manifestations of stomach content reflux have only recently started being seen as important based on the assumption of their important role in causing respiratory tract diseases.

In clinical practice, LPR is mostly not recognized because it may be a "silent reflux" and diagnostic and therapeutic protocols are still inadequate, so proper treatment is usually delayed. Laryngeal symptoms are the most common, so patients are managed by otolaryngologists. Indeed, otolaryngologists have developed the diagnostic Reflux Symptom Index (RSI) questionnaire based on the importance of certain disease symptoms and the Reflux Finding Score (RFS) based on frequency of pathological changes determined by laryngoscopy (15). On the other hand, considering the high prevalence of the disease and uncharacteristic clinical image, most patients report to their family medicine physicians (14-17). For family medicine physicians LPR represents an important medical problem and a challenge in fast diagnostics, proper treatment, and proper selection of patients who require additional multidisciplinary diagnostic procedures. Knowledge of pathogenic pathway of the disease and its clinical manifestations can help physicians in creating an adequate program for prevention, early diagnosis, and adequate therapy for LPR. In particular, it has to be considered that untreated LPR can be one of the etiological causes of laryngeal cancer.

The development of the disease can be benign or malignant and life threatening, and all of its forms can considerably affect life quality in patients. Laryngeal pathological changes could be discovered with laryngoscopy, and some even with detailed esophagogastroscopy. These changes may include: oedema, hyperaemia, or erythema of the vocal chords and laryngeal edges, ventricular obliteration, granulation, presence of dense endo-laryngeal secretion. and hypertrophy of the posterior commissure (10,15). As consequence, an appropriate diagnosis of LPR represents a challenge for general practitioner and specialists.

A large number of clinical studies confirmed low specificity and sensitivity of diagnostic tests such as laryngoscopy, esophagogastroscopy, proximal pH monitoring (hypopharyngeal and oropharyngeal). Evaluation of symptoms using the Reflux Symptom Index is considered to be the basic diagnostic procedure. A newer method of measuring salivary pepsin (Pep-test) can confirm LPR diagnosis because its sensitivity and specificity is 87% (13). In this regard, it has to be noted that pepsinogen is produced only in the stomach, so pepsin may be envisaged as a specific biomarker for gastric reflux. The Pep-test is a fast and non-invasive method and could have a wide variety of uses in primary health care.

LPR therapy is complex and requires also modification of the patient's lifestyle and habits. Body weight reduction and physical activity, quitting cigarettes and alcohol use are one of the first steps in lowering the intensity of symptoms in patients (17). Nutritional interventions with correct food choices and bowel movement regulation lead to lowering dyspeptic complains, but also lower the number of reflux episodes. Emptying of the bowels causes lower intra-abdominal pressure, which leads to lower possibility of stomach content reflux into the oesophagus, larynx and pharynx. Obesity, or more precisely high BMI, so including overweight, is an independent factor in stomach reflux occurrence because of its specific effect mechanism on the gastroesophageal juncture (17). LPR treatment and management is supposed to reduce the acidity or stomach contents and neutralize acid-peptic activity in larynx, pharynx and oesophagus. High dosages of PPI (proton pump inhibitors) have shown the best effects in reducing reflux in the course of 24

hours. Alkaline water and alginates show a positive additional effect in lowering acid-peptic activity in the larynx and pharynx. Patients are supposed to have long-term treatment during the course of 6 months because of high sensitivity of the mucosal membrane in the stomach and pharynx. Difficult cases with a proven hiatal hernia can be considered for surgical treatment as well (6).

Therefore, acid suppression is the mainstay of therapy for gastric reflux, and proton pump inhibitors (PPIs) are the most potent drug in this field (18,19). Although PPIs are the treatment of choice for GERD, still approximately one-third of patients with GERD fail to respond symptomatically to a standard dose PPI, either partially or completely (20). Actually, NERD accounts for 60–70% of GERD patients and is considered the most common presentation of GERD. However, only approximately 30–40% of NERD patients respond to a standard dose of PPIs, much lower than that in erosive esophagitis, and the low response rate to PPIs in NERD patients is the main contributor to the high portion of PPI failure phenomenon in GERD, and also LPR, management (21). The mechanisms of failure of PPI therapy are complex and multifactorial (20,22-24). Consequently, other medications should be considered and used. In this context, alginates and histamine type-2 receptor antagonists (H2RAs) may provide additional benefit for symptom relief in patients with persistent symptoms despite PPI therapy and can be considered as add-on therapy for patients who fail with a PPI. However, because of the concern about tolerance, H2RA is suggested to be taken on demand or intermittently.

PPI-refractory GERD (and LPR), defined as persistent reflux symptoms not responding to a double dose of a PPI therapy during a treatment period of at least 12 weeks, is an important issue in clinical practice and poses a great challenge for general practitioners, internists, gastroenterologists, and otolaryngologists (20). Compliance with therapy should be checked first by the physician, and the presence of functional gastrointestinal disorders, psychologic distress, functional heartburn or other esophagitis not related to reflux should also be carefully evaluated in these patients.

On the basis of these concepts, alginate may be considered a fruitful and relevant option in many patients with reflux disease. In particular, the knowledge about the utility of alginates derives from an interesting research area investigating the pathogenic role of the so-called “acid pocket”. The acid pocket is a short zone of unbuffered highly acidic gastric juice that accumulates in the proximal stomach after meals. Serving as the source of acid reflux, the acid pocket increases the propensity for acid reflux by all conventional mechanisms, such as TLESR and hiatus hernia, and has been considered as an important cause of GERD (25, 26). Alginate is an anionic polysaccharide occurring naturally in brown algae and has a unique property in the treatment of gastric reflux by eliminating the acid pocket. Alginate-antacid formulation can reduce postprandial symptoms by neutralizing the acidity of gastric contents.

In addition to neutralizing the gastric acidity, more importantly, alginate and bicarbonate, usually contained in an alginate-based formulation, form a foamy gel that is like a raft floating on the surface of gastric contents after interacting with gastric acid, and this barrier-like gel displaces the acid pocket from the oesophageal-gastric junction and protects both the oesophageal and the upper respiratory mucosa from the acid and non-acid reflux by gel coating (27-30). Like an antacid, an alginate-based formulation demonstrates an immediate onset of effect within 1 h of administration, which is faster than a PPI and H2RA (31). Compared with antacids, an alginate-based formulation is more effective than an antacid in controlling postprandial oesophageal acid exposure and quickly relieving reflux symptoms, including heartburn, regurgitation, vomiting and belching, with longer duration (32-34).

Alginate-based formulations are also non-inferior to omeprazole in achieving a heartburn-free period in moderate episodic heartburn (35). Therefore, alginate has the special properties of protection of the oesophageal and upper respiratory mucosa from acid and non-acid reflux and displacement of acid pocket away from the oesophagus, all of which make alginate an attractive agent in the management of refractory reflux symptoms with a cause other

than by acid, such as NERD (36). Compared with placebo, an alginate-antacid formulation demonstrated superior relief of reflux symptoms including heartburn and regurgitation in both patients with NERD and erosive esophagitis in a double-blind randomized controlled trial (37). In another double-blind randomized clinical trial comparing the efficacy of alginate to omeprazole in patients with NERD, alginate demonstrated non-inferiority to omeprazole and was as effective as omeprazole for symptomatic relief (38).

Furthermore, adding alginate to a PPI can significantly relieve heartburn compared to using a PPI alone in patients with NERD, suggesting an additional benefit of alginate as add-on therapy in the management of refractory symptoms (39).

Interestingly, in a meta-analysis study, six of nine randomized trials found no difference between the PPI and placebo groups for LPR, whereas three trials exhibited statistically significant results (1). In a systemic review, three of four randomized controlled studies revealed that prokinetic agents significantly reduced LPR symptoms, but there were too many study limitations to draw firm conclusions (40). In a small randomized controlled study, a liquid alginate suspension could achieve significant improvement in the symptom scores and clinical findings of LPR (41).

Therefore, on the basis of this discussed background, the management of suspected LPR is intriguing as it is very difficult, if even possible, to make a definitive diagnosis with the tools currently available (42). If there is no doubt that many patients do have LPR symptoms, the probability of suspecting LPR, especially when typical reflux symptoms are lacking and PPIs do not improve symptoms, are low, mainly in non-specialist setting. LPR management is responsible of high economic burden mainly related to the prescription of PPIs, which may be, in most cases, not justified (43-45). Therefore, in patients, initially visited by GP, who do not respond to a 2 to 3-month course of double dose PPI therapy, the role of the otolaryngologist is to document the presence of signs and symptoms suggestive of LPR with appropriate (i.e. validated and reproducible) investigations, namely fiber-endoscopy, and validated questionnaire (for example RSI and RFS).

If LPR is documented, it is reasonable empirically testing these patients on PPIs to check for reflux control may be useful to select PPI-responder patients. If PPI are not adequate to control symptoms an add-on treatment should be prescribed. On the basis of the above-mentioned concepts, alginate could be a first-choice option. As a matter of the fact, as there is no specific and focused medication able to irreversibly inactivate pepsin and block acid production, other compounds have place in LPR management, including medical devices with barrier effect. In the current scenario, an effective supportive strategy may be constituted by compounds able to strengthen the epithelial barrier providing protection from acid and pepsin and promoting mucosal healing. In other words, an old concept could be revised for LPR therapy: the "cytoprotection" of mucosal tissues (46). Mucosal cytoprotection was an ideal target of two main drug classes: prostaglandins and sucralfate. Many clinical trials supported this theory that met favourable impression some decades ago (47-50).

Presently, the newest alginate compounds renowned the interest in this attracting and stimulating area. In this regard, a new medical device (Marial®), unique still now possessing the indication for both GERD and LPR, has been recently launched in the Italian market. It is an innovative gel compound, containing magnesium alginate and E-Gastryal® (hyaluronic acid, hydrolysed keratin, Tara gum, and Xantana gum).

E-Gastryal® is a complex of phyto-polymers, Tara and Xantana gums, that are natural polysaccharides with high molecular weight and partially hydrosoluble, and able to provide viscosity to the solution and to generate a support frame where keratin peptide chains and hyaluronic acid anchor. Hyaluronic acid (HA) is a biopolymer with medium molecular weight characterized by optimal hygroscopic and hydrodynamic features. The chemical-physical properties of the polymeric complex confer muco-adhesiveness to E-Gastryal® so increasing the contact surface and the residence time on the mucous membranes of larynx, pharynx, and oesophagus. In this context, hyaluronic acid is

extremely bioavailable and able to carries out its activity aimed to induce repairing and regenerating the damaged epithelium. HA, by its hydrophilic essence, realizes a favourable milieu for cellular migration; in addition, HA, having a scavenger activity of free radicals, exerts a protective role towards oxide damage and proteolytic enzymes, such as pepsin.

Hydrolysed keratin, an indigestible substance, increases the solidity and the resistance of E-Gastryal®, enhancing the barrier effect. Really, keratin abounds with cysteine, amino acid sulphide, that forms disulphide bridges extremely firm and able to link the amino acid chains, making an helical structure characterized by difficult dissolution and resistant to attack of acid and pepsin. The alginate has the peculiar property of a boating raft at the acid pocket and selectively inhibits pepsin by mannuronic acid, highly contained in the specific alginate (51). In particular, this medical device contains Magnesium alginate with high ratio mannuronic acid/glucuronic acid and with raised viscosity shaping a stable and compact raft. As the new NICE guidelines on digestive reflux pointed out the relevance of using medicines alternative to PPI (52,53), a preliminary experience was conducted on patients with LPR and GERD (54). This study provided evidence that the introduction of Marial® as add-on was able to induce a clinically relevant improvement.

For these reasons, two large surveys were conducted in Italy, involving both otolaryngologists and gastroenterologists. The aims were to define the patients' characteristics, including the clinical features, the assessment of treatments, and new therapeutic approaches in view of the new medical device Marial®. Therefore, the current Supplement reports and discusses the outcomes of these two very large surveys, conducted in real-world settings.

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