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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.

Key words: gastric reflux, GERD, laryngo-pharyngeal reflux, Marial®

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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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RELIEVING LARYNGOPHARINGERAL REFLUX (RELIEF) SURVEY IN OTOLARYNGOLOGY - THE VIEWPOINT OF THE OTORHINOLARYNGOLOGIST

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Laryngopharyngeal Reflux (LPR) should be considered as part of extraesophageal reflux (EER). This reflux involves respiratory structures other than, or in addition to, the oesophagus. A new medical device for the treatment of gastric reflux, including LPR, has been launched in Italy: Marial®. Therefore, the aim of the present survey was to analyse the prescriptive behaviour both considering the past or current treatments and clinical features during a specialist routine visit. The current survey was conducted in 86 Otorhinolaryngological centers, distributed in all of Italy. Globally, 4.418 subjects [47% males and 53% females, 50.1 (14.5) years-of-age] were visited. The visits included laryngoscopy, Reflux Finding Score (RFS) and Reflux Symptom Index (RSI) questionnaires. The total RSI median score was 15 (12-19) and the total median RFS value was 10 (8-12). Interestingly, a significant change in the new drug prescription was observed ($p<0.0001$): over two-third of patients (67%) received Marial® as monotherapy, whereas PPI plus add-on were prescribed to almost one-third of the patients. PPI alone was prescribed in less than 1%. In conclusion, LPR is a common disorder characterized by typical signs and symptoms; LPR patients may be correctly identified and scored by evidence-based criteria. In addition, the present survey reported that LPR treatment has been considerably changed by the introduction of a new medical device.

Reflux of gastric gaseous contents into the oesophagus, such as the gastroesophageal reflux, is usually considered as a physiological phenomenon occurring in all subjects, mainly after meals. Brief and infrequent exposure of the oesophagus to gastric contents does not usually result in injury and disease, implying that there are intrinsic mechanisms of defence acting to maintain esophageal mucosal integrity. Actually, pH-monitoring studies demonstrated that up to 50 reflux episodes a day (below pH 4) could be considered normal (1, 2). Esophageal symptoms and complications arise when reflux is prolonged and/or the defence mechanisms defect, making an individual more susceptible to harm from the gastric refluxate. This condition is defined gastroesophageal reflux disease (GERD). GERD is the most common chronic disease of adults in the United States and affects more than 30% of individuals in Western

Key words: gastric reflux, GERD, laryngo-pharyngeal reflux, Marial®

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society (3). Moreover, if gastric refluxate moves more proximally into the laryngopharynx, it is called laryngopharyngeal reflux (LPR). LPR should be considered as part of extraesophageal reflux (EER), reflux involving structures other than, or in addition to, the oesophagus, and airway reflux involving proximal gastric reflux into the airways.
LPR contributes to several otorhinolaryngologic symptoms and inflammatory disorders, and probably also to neoplastic diseases of the laryngopharynx, and it seems to be also as common in children and infants as adults. It is estimated that 10% of patients visiting otorhinolaryngology clinics have reflux-attributed disease, and up to 55% of patients with hoarseness have reflux into their laryngopharynx (4). In particular, there are many epidemiological studies that reported high prevalence of LPR: up to 60% of selected populations (5-9), therefore LPR may be considered one of the most common factors associated with inflammation in the upper airways.

From a diagnostic point of view, it is to note that LPR may exist also without GERD: the so-called "silent reflux". As consequence, the work-up is not easy and there are no gold standard diagnostic criteria. Usually, LPR is diagnosed on a clinical ground, such as based on typical symptoms that may suggest LPR as reported in the introductive paper of the current Supplement. So, history is the mainstay in the LPR management. The Position Statement of the American Academy of otolaryngologists identified the most common symptoms of LPR: hoarseness, *globus pharyngeus*, dysphagia, cough, chronic throat clearing, and sore throat (7). These clinical symptoms identifiable on initial history taking became part of algorithms to assess and manage LPR. Potential diagnosis of LPR based on symptoms depends on aggregating multiple different symptoms to create a composite score, which could better reflect presence or absence of reflux.

Belafsky proposed the reflux symptom index (RSI) asks about symptoms such as hoarseness, throat clearing, cough, and heartburn to create a composite score whereby an RSI>13 suggests LPR (10). Another approach to LPR diagnosis is based on laryngopharyngeal appearance to judge whether pathophysiologic reflux is or is not present. Rather than using generalized appearance of overall erythema or oedema alone, a systematic approach involving discrete scoring of possible inflammation at various locations within the larynx has been proposed: the reflux finding score (RFS), with a RFS >7 thought to be suggestive of LPR (11). However, both RSI and RFS might be not exhaustive in some patients. Other diagnostic tools include pH-metry, digestive endoscopy, imaging, pepsin assay, and empiric medication trial. This last point is very common in clinical practice. In fact, the *ex juvantibus* treatment of patients with suspected gastric reflux with proton pump inhibitors (PPI) has revolutionized the management of GERD (12).

The rising cost in treatment of LPR is in large part due to the prevailing practice of empiric treatment for patients whose history and physical examination suggest LPR. On the other hand, despite the amount of money being spent in care of patients with presumed LPR, patient satisfaction may remain poor. In this regard, Francis and colleagues reported that only 54% of patients reported improvement despite the many diagnostic procedures, evaluation by both gastroenterologists and otolaryngologists, and medical management that they received (8). The fact that patients are not reporting symptomatic improvement, even though PPIs suppress gastric acid production well, suggests that the diagnosis of LPR may be inaccurate. Supporting this impression, there are studies showing that PPI may be no more effective than placebo in treatment of patients with symptoms suggestive for LPR diagnosis (13).

Interestingly, a closer look at this meta-analysis shows that individual studies which exclude patients with heartburn are least likely to show benefit of PPI in patients with possible LPR, while those studies which investigate patients with possible LPR in the setting of typical GERD symptoms are perhaps more likely to show benefit (2). As PPI could not be resolved in many LPR patients, alternative medications are prescribed. Alginates represent an interesting option in LPR treatment as outlined and discussed in the Introduction of the current Issue. Very recently, a new medical device has been introduced in the Italian market: Marial® (manufactured by Aurora, Milan, Italy) containing

magnesium alginate and E-Gastryal®. For this reason, an Italian survey explored the pragmatic approach of a group of otorhinolaryngologists in the LPR management.

The aim of this survey was to analyse the prescriptive behaviour both considering the past or current treatments and clinical features during a specialist routine visit.

MATERIALS AND METHODS

The current survey was conducted in 86 Otorhinolaryngological centers, distributed in the whole Italy, so assuring a wide and complete national coverage. Otorhinolaryngologists were recruited to participate in the study. They endorsed to the Project RELIEF (Relieving LPR in Otolaryngology). They were asked to recruit all consecutive patients visited because of upper respiratory symptoms ascribable to a suspected LPR.

- Patients were visited and completed the RSI questionnaire. Laryngoscopy was performed in most patients (3,932) and RFS was calculated.
- RSI was evaluated according to the protocol proposed by Belafsky (10). Items are analytically reported in Table I.
- RFS was evaluated according to the protocol proposed by Belafsky (11). Items are analytically reported in Table II.

Past or current treatment was recorded and analysed. As several possible combinations of treatment regimens

Table II. *Reflux Finding Score.*

Subglottic oedema	0 = absent
	2 = present
Ventricular oedema	2 = partial
	4 = complete
Erythema/hyperaemia	2 = arytenoids only
	4 = diffuse
Vocal-fold oedema	1 = mild
	2 = moderate
	3 = severe
	4 = polypoid
Diffuse laryngeal oedema	1 = mild
	2 = moderate
	3 = severe
	4 = obstructing
Posterior commissure hypertrophy	1 = mild
	2 = moderate
	3 = severe
	4 = obstructing
Granuloma/granulation tissue	0 = absent
	2 = present
Thicken laryngeal mucus	0 = absent
	2 = present

RFS: *Reflux Finding Score;* ***RFS>7:*** *suspect of LaryngoPharyngeal Reflux (LPR).*

Table I. *Reflux Symptom Index.*

Within the last month, how did the following problems affect you?	0 = no problem 5 = severe problem					
1. Hoarseness or a problem with your voice	0	1	2	3	4	5
2. Clearing your throat	0	1	2	3	4	5
3. Excess throat mucus or postnasal drip	0	1	2	3	4	5
4. Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
5. Coughing after you ate or after lying down	0	1	2	3	4	5
6. Breathing difficulties or choking episodes	0	1	2	3	4	5
7. Troublesome or annoying cough	0	1	2	3	4	5
8. Sensation of something sticking in your throat or a lump in your throat	0	1	2	3	4	5
9. Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5
RSI > 13 = Abnormal	Total					

RSI: reflux symptom index.

could be prescribed, an arbitrary restriction was decided. So, 3 main options were considered: PPI alone, PPI plus add-on treatment (mainly alginates), and alginates alone. The same subdivision was adopted for new treatments prescribed during the visit. As the survey was based on a real-world practice, doctors had the complete liberty of choosing the medications on the basis of the best practice.

Demographic and clinical characteristics were described using means with SDs for normally-distributed continuous data (i.e. age) or medians with lower and upper quartiles for not normally-distributed data (i.e. for RSI or RFS) or as absolute frequency and percentages for categorical data (i.e. frequency of patients' RSI+ or RFS+).

Any statistically significant difference in the median values of each continuous variable between normal and pathological patients (as defined at the RSI or RFS questionnaire) was evaluated with the Mann-U Whitney test. When more than two groups were compared, Kruskal Wallis test, followed by Dunn's test, was used.

Comparison of frequency distributions was made by means of the chi-square test or the Fisher's exact test in case of expected frequencies <5. Statistical significance was set at $p < 0.05$, and the analyses were performed using GraphPad Prism software, GraphPad Software Inc, CA, USA.

RESULTS

Globally, 4.418 subjects [47% males and 53% females, 50.1 (14.5) years-of-age] were visited in the 86 Italian ORL centers. Interestingly, only 33% (1.454) of patients had a previous LPR diagnosis, whereas 67% of subjects were never evaluated. The percentage of patients with recognized LPR increased accordingly to the age (data not shown). In addition, most of patients with LPR diagnosis were visited and assessed within the last years.

All subjects completed the RSI questionnaire. On the contrary, laryngoscopy and RFS were evaluated in 3.932 subjects.

Globally, 2.805 (63.5%) patients had positive RSI score, such as >13. RSI values for each single symptom are analytically reported in Fig. 1. The symptom with the highest score was the throat

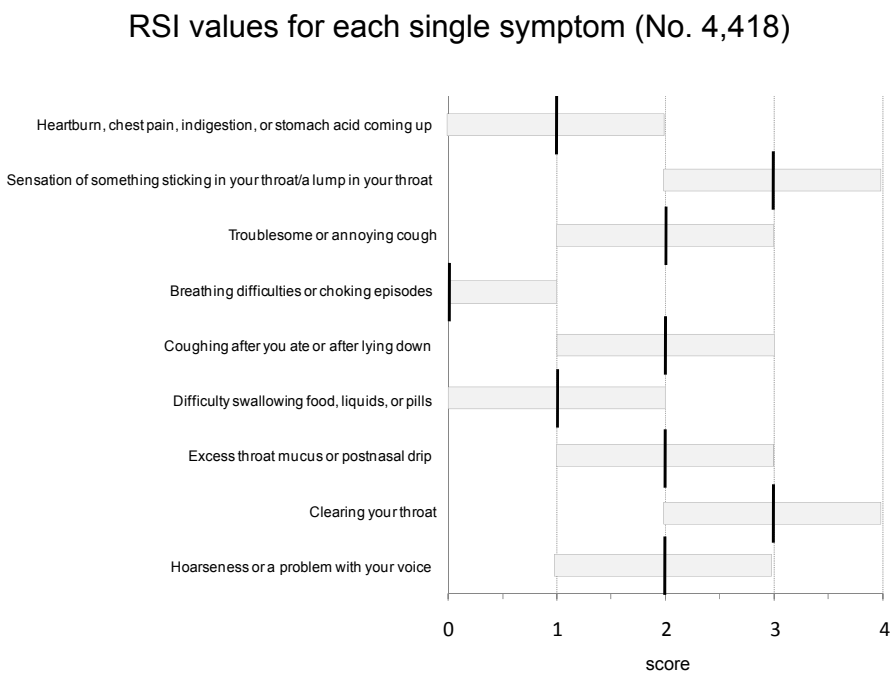

Fig. 1. *Reflux symptom index (**RSI**) as median values for each single symptom in the whole population (No. 4.418) (**panel A**) or as median" total" values in the whole population (No. 4.418) and in RSI+ or RSI- patients (**panel B**). Score are reported as medians (**bars**) with lower and upper quartiles (**boxes**).*

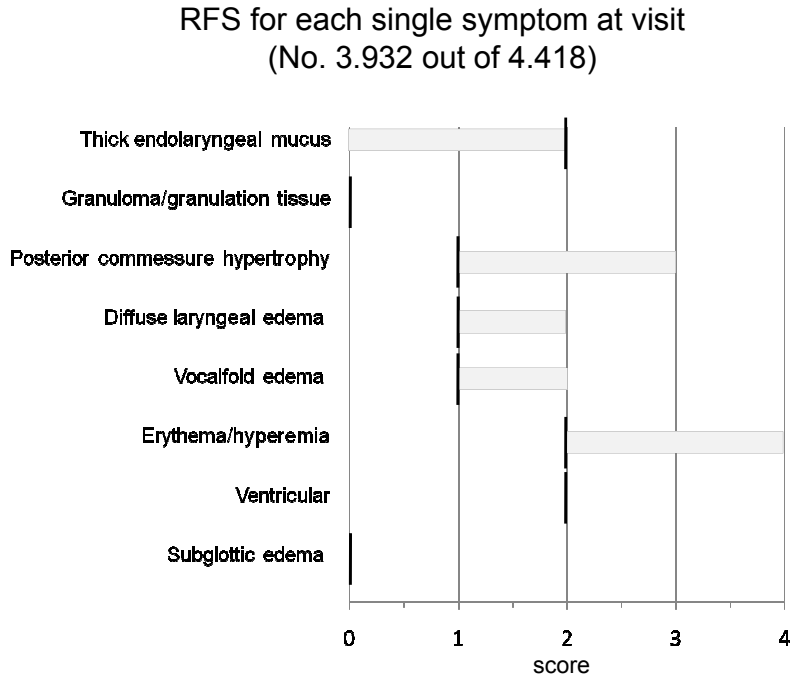

Fig. 2. *Reflux finding score (RFS) as median values for each single symptom in the whole population (No. 3.932)* ***(panel A)*** *or as median" total" values in the whole population (No. 3.932) and in RSI+ or RSI- patients* ***(panel B)****. Score are reported as medians* ***(bars)*** *with lower and upper quartiles* ***(boxes)****.*

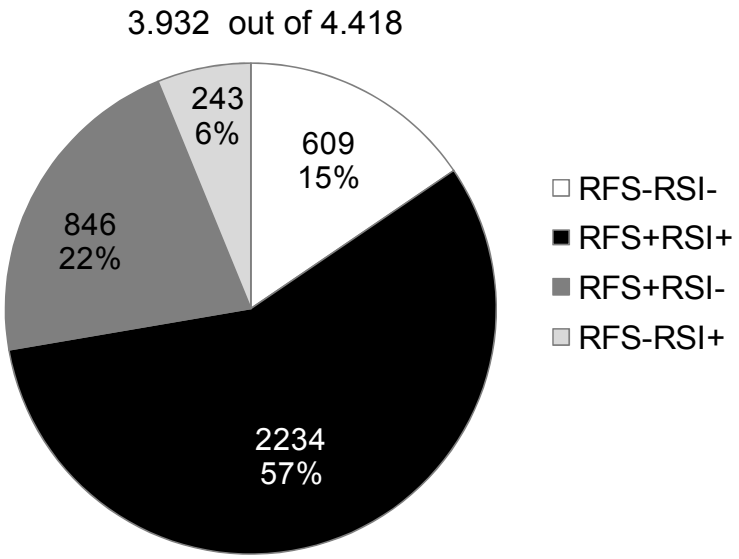

Fig. 3. *Distribution of patients according to the positivity or negativity to RFS (score >7) and to RSI (score >13): RSI+RFS+; RSI+RFS-; RSI-RFS+; and RSI-RFS.*

clearing, but laryngospasm had the lowest score. The total RSI median score was 15 (12-19) in the whole population and 18 (16-23) in RSI+ patients and 10 (8-12) in RSI- patients respectively ($p<0.0001$).

RFS values for each single sign are analytically reported in Fig. 2. The sign with the highest score was the larynx hyperaemia, but subglottic oedema and granuloma/granulation tissue were absent in all subjects. The total median RFS value was 10 (8-12) in the whole population and 11 (9-13) in RFS+ patients and 6 (5-7) in RFS- patients respectively ($p<0.0001$).

Patients were subdivided in 4 categories considering the positivity (or negativity) to RFS (score >7) and RSI (score >13), so the subgroups are: RSI+RFS+; RSI+RFS-; RSI-RFS+; and RSI-RFS-. As reported in Fig. 3, 2,234 subjects (57%) belonged to RSI+RFS+ subgroup; 846 (22%) to RSI-RFS+; 609 (15%) to RSI-RFS-; and 243 (6%) to RSI+RFS-.

RSI+RFS+ patients had median RSI 18.0 (16-23) and median RFS 11.0 (10-14); RSI-RFS+ patients had median RSI 11.0 (9-12.5) and median RFS 10.0 (9-12); RSI+RFS- patients had median RSI 16.0 (14-19) and median RFS 7 (6-7); RSI-RFS- patients had median RSI 9.0 (7-11) and median RFS 6.0 (5-7). There was a significant difference among subgroups in RSI and in RFS values ($p<0.0001$): patients with RFS+ and RSI+ had highest scores, as reported in Fig. 4. Noteworthy, 638 patients presented conjunctival hyperaemia, and 1538 rhinopharyngeal hyperaemia.

Fig. 5 shows the distribution of the patients considering the treatments: past, current or never: 1540 patients (39%) were previously treated: 908 (24%) in the past and 632 (16%) currently, whereas 2277 (60%) patients were still untreated at the visit.

The different types of treatments prescribed in the past or currently used are reported in Fig. 6A, B respectively. We considered 3 subgroups: monotherapy with PPI, PPI plus add-on, and Miscellany. Add-on therapy included anti-acidic or anti reflux treatment, alginates or prokinetics. Miscellany included anti-acidic or anti reflux treatment, alginates or prokinetics. Most of patients were treated with PPI as monotherapy (about 70%) and about 20% had PPI plus add-on therapy.

Fig. 7 shows changes in the distribution of the medications: Marial® as monotherapy, PPI as monotherapy or PPI plus add-on in current treatments

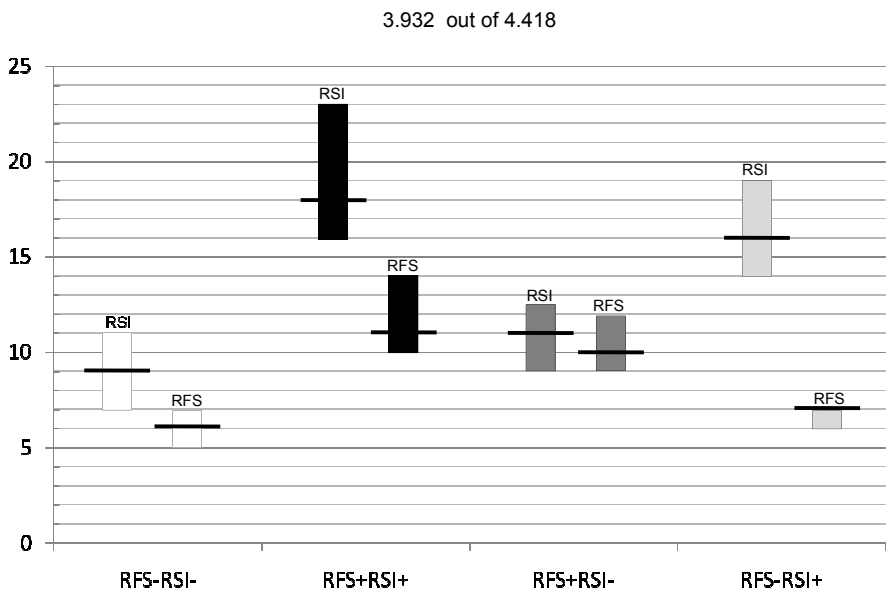

Fig. 4. *Median values of total RSI and total RFS in each of 4 subgroups according to the positivity or negativity to RFS (score >7) and to RSI (score >13): RSI+RFS+; RSI+RFS-; RSI-RFS+; and RSI-RFS (score >13): RSI+RFS+; RSI+RFS-; RSI-RFS+; and RSI-RFS.*

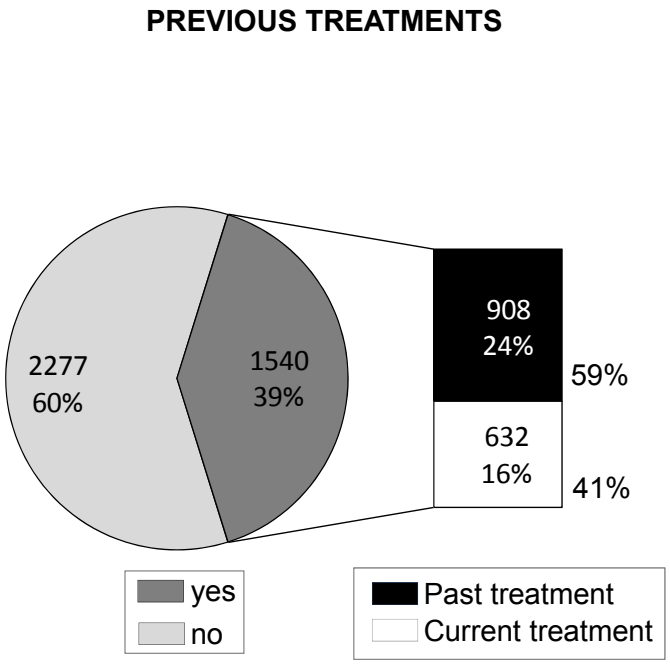

Fig. 5. *Distribution of the 3.932 patients according to the treatments: past, current or never.*

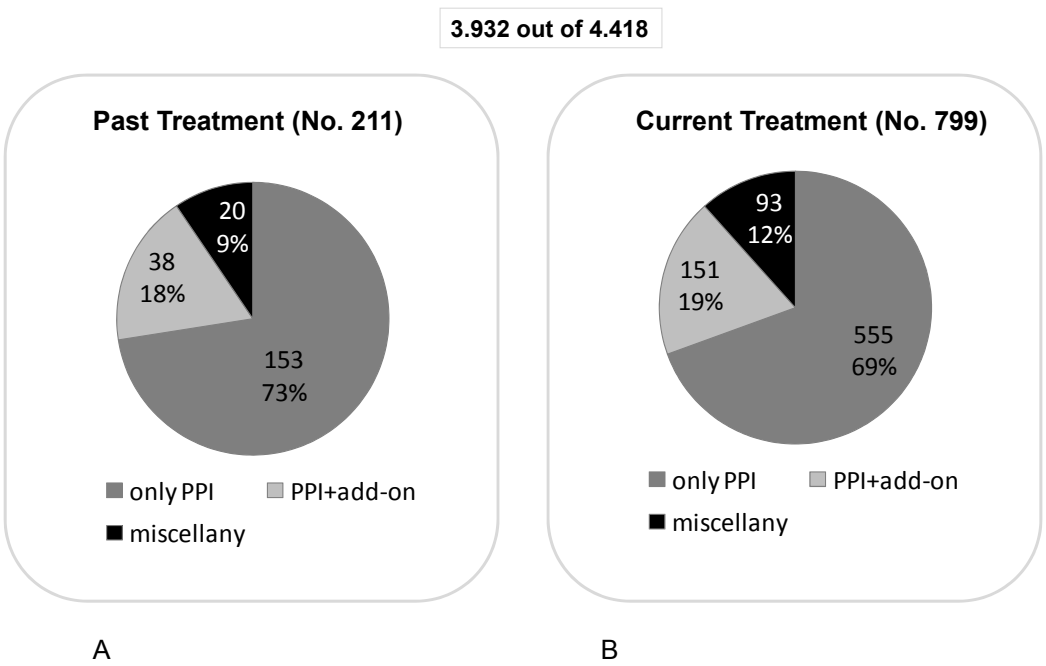

Fig. 6. *Distribution of different types of treatments prescribed in the past (**panel A**) or currently used (**panel B**): monotherapy with PPI, PPI in add-on, and Miscellany.*

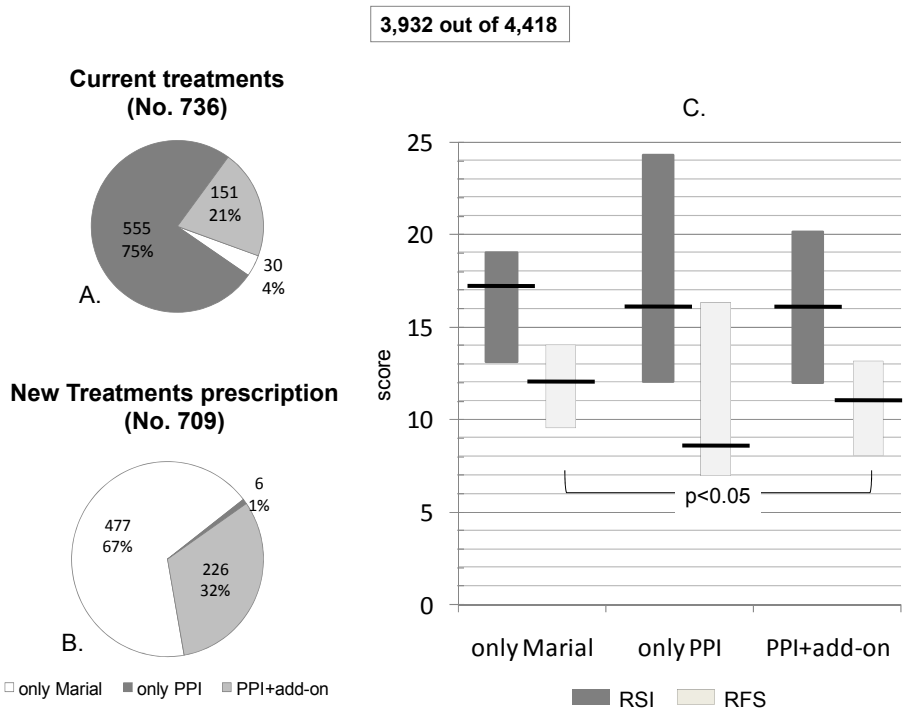

Fig. 7. *Changes in the distribution of Marial® as monotherapy, PPI as monotherapy or PPI in add-on in current treatments (**panel A**) and in new prescribed treatments (i.e. prescription during the visit) (**panel B**). **Panel C** reports median RSI and RFS values in the 3 subgroups of treatments*

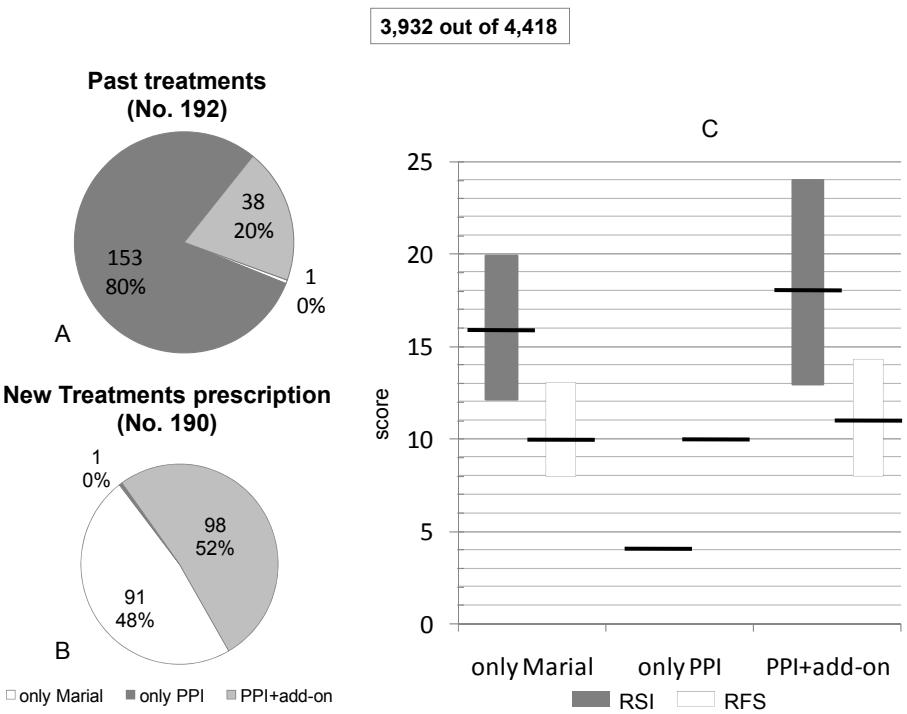

Fig. 8. *Changes in the distribution of Marial® as monotherapy, PPI as monotherapy or PPI plus add-on in past treatments (panel A) and in new prescribed treatments (i.e. prescription during the visit) (panel B). Panel C reports median RSI and RFS values in the 3 subgroups of treatments.*

(Fig. 7A) and in new prescribed treatments (i.e. prescription during the visit) (Fig. 7B). PPI as monotherapy was the most frequent treatment as current treatment (75%). After the visit, a significant change in the drug prescription was observed ($p<0.0001$): over two-third of patients (67%) received Marial® as monotherapy, whereas PPI plus add-on were prescribed to almost one-third of the patients. PPI alone was prescribed in less than 1%. No statistically significant difference was detected in RSI among the three treatment groups ($p=0.25$) (Fig. 7C); differently, RFS values differ among the three groups ($p=0.027$) being significantly different in Marial® as monotherapy and in PPI as add-on treated patients ($p<0.05$).

Comparison between the distribution of Marial® as monotherapy, PPI as monotherapy or PPI plus add-on in past treatments (Fig. 8A) and in new prescribed treatments (i.e. prescription during the visit) (Fig. 8B) are reported in Figure 8. As for current treatment, also for past treatment, PPI as monotherapy was administered to 80% of patients. Again, after the visit, a significant change in the drug prescription was observed ($p<0.0001$): about half patients received Marial® as monotherapy or PPI plus add-on. Again, a very limited proportion of patients received PPI in monotherapy. No statistically significant difference was detected in RSI ($p=0.059$) or RFS ($p=0.49$) among the three treatment groups (Fig. 8C).

Finally, Fig. 9 shows the new treatments prescribed to all patients when discharged: Marial® as monotherapy was prescribed in 2.896 (69.8%) patients, PPI alone in 12 (0.3%), and PPI plus add-on in 1.239 (29.9%).

DISCUSSION

Gastric reflux, encompassing the Gastroesophageal Reflux (GER) and the Laryngopharyngeal Reflux (LPR), is a common medical disorder that occurs in up to 40% of selected population and with increasing prevalence over time (15, 16). Gastroesophageal reflux is characterized by two main symptoms: heartburn and regurgitation. Moreover, extraesophageal manifestations may appear and are related to the underlying gastric reflux. In this regard, the Montreal Classification includes upper airways symptoms, such as hoarseness, sore throat, globus sensation, throat clearing, and lower airways

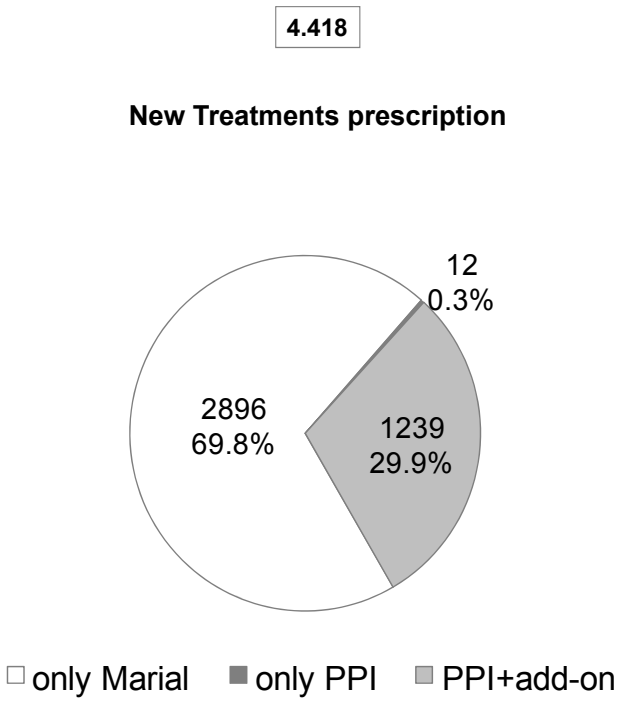

Fig. 9. *New treatments prescription in the whole population.*

symptoms, such as cough and breathlessness (17). When the gastroduodenal refluxate arrives besides the oesophagus, chronic laryngeal and pharyngeal symptoms and signs may arise; they define the LPR (18). LPR may present as isolate manifestation of gastric reflux, without digestive symptoms, the so-called ”silent reflux”. In this case, the use of acid suppressive medication might be contraindicated (19). As there is no gold standard diagnostic method, the LPR diagnosis may be difficult in clinical practice. In this regard, otorhinolaryngologists have conceived some diagnostic tools able to identify patients with suspected LPR. They include: laryngoscopic examination, specific questionnaires, such as RSI and RFS, and in routine setting empiric treatment addressed to suppress acid aggression and to protect upper respiratory mucosal tissue.

PPI are the most prescribed medication in the treatment of gastric reflux, but PPI may be also ineffective in some patients, and may have also side effects, and are expensive. As alternative/add-on option, alginates may constitute a valid resource in clinical practice (20-23). Very recently, a new medical device has been introduced in the Italian market: Marial®, containing E-Gastryal® and magnesium alginate. This compound boasts interesting features: it generates a raft contrasting acid pocket, repairs mucosal injuries, and protects upper respiratory epithelium. For these reasons, an Italian survey on otorhinolaryngologists has been conducted to define prescriptive characteristics in a real-world setting.

The present findings allow to deduce important considerations, useful in clinical practice, mainly concerning the wide cohort of patients enrolled. First, a very high percentage of patients had positive RSI score. The most frequent symptom was throat clearing. This information may be useful in clinical practice and deserves adequate analysis. Likewise, many patients were RFS+ and the most common signs were larynx hyperaemia and ventricular oedema. On the basis of RSI and RFS scoring, the most numerous subgroup had both parameters positive. Interestingly, these patients had the highest score for both diagnostic methods. This information may be clinically relevant as could identify the subjects with more severe clinical features.

Considering past and current treatments for LPR, PPI was surely the most common prescribed medication, preferably as monotherapy and rarely integrated by an add-on treatment. The arrival of Marial® on the market seems to have profoundly modified the prescriptive behaviour of otolaryngologists, at least the physicians involved in the present survey. In fact, most prescription envisaged Marial®, mainly as monotherapy. On the contrast, PPI were usually prescribed in association with Marial®.

The current survey has some limitations, including the open design, the lack of a follow-up, the lack of functional, macroscopic and microscopic evaluation, and imaging techniques, and the lack of biomarkers (eg pepsin) measurement. In addition, the survey was conducted in a real-world setting, so there are some discrepancies in reported outcomes due to the lack of some data. Therefore, further studies should be conducted to addressed these unmet needs. On the other hand, the strength of this survey was the high number of enrolled patients and the use of validate and consolidated diagnostic criteria, including RSI and RFS scores, the last based on an objective evaluation of signs (laryngoscopy).

In conclusion, LPR is a common disorder characterized by typical signs and symptoms; LPR patients may be correctly identified and scored by evidence-based criteria. In addition, the present survey reported that LPR treatment has been considerably changed by the introduction of a new medical device.

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RELIEVING LARYNGOPHARINGERAL REFLUX (RELIEF) SURVEY IN OTOLARYNGOLOGY - II THE VIEWPOINT OF THE PATIENT

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As LPR diagnostic work-up is complex in the absence of a definitive gold standard diagnostic test, patient symptoms have become a primary method to identify those with LPR. In this regard, Reflux Symptom Index (RSI) is a reliable self-administered questionnaire useful also to monitor changes after treatment. An Italian survey on patients with LPR evaluated the effect of treatments for LPR that were prescribed in a real-world setting, such as Otolaryngological clinics. In this part of the survey, 1,680 subjects [45.2% males, 54.8% females, 50.4 (14.7) years] were visited in the 86 Italian ORL centers. About 70% of patients were treated with Marial® alone, 27% with PPI plus add-on. RSI change assessment was the primary outcome. Both therapeutic options significantly ($p<0.0001$) reduced RSI score interestingly since the second week. The inter-group comparison demonstrated the Marial® monotherapy induced a greater reduction of RSI than PPI plus add-on since the second week. In conclusion, the present survey reported that a new medical device (Marial®) may be considered a valid option for the treatment of LPR.

Laryngopharyngeal reflux (LPR) is an extra-esophageal manifestation of gastroesophageal reflux disease (GERD) as stated by the Montreal Consensus (1). GERD epidemiological prevalence is worldwide increasing (2, 3). Consistently, the number of patients who are aware of unusual sensations in the laryngopharynx with GERD is also increasing (4, 5). LPR has a relevant impact in otolaryngologist practice: up to 50 % of patients with voice complaints could have LPR (6). Moreover, LPR has been associated with several disorders, including reflux laryngitis and reflux cough. Symptoms associated with reflux laryngitis are hoarseness, throat clearing, choking sensation, dysphagia, dysphonia, laryngeal globus, sore throat, and laryngospasm. Noteworthy, LPR is not usually associated with esophagitis, heartburn, or regurgitation (7). Since the typical LPR symptoms are nonspecific and can also be caused by infections, vocal abuse, allergy, smoking, inhaled environmental irritants, alcohol abuse, chronic sinusitis, laryngeal cancer, thyroid disorder, drugs, psychosomatic disorder, and depression, increased

Key words: gastric reflux, GERD, laryngo-pharyngeal reflux, Marial®

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awareness of LPR can lead to overdiagnosis or mysdiagnosis of the disease (4).

The LPR diagnostic work-up is pragmatically based on history, clinical examination, and laryngoscopy. In addition, 24-hour pH monitoring, pepsin assay, digestive endoscopy, and imaging may be considered, but they are usually reserved to complicated patients in clinical practice. On the contrary, protonic pump inhibitor (PPI) test, such as an empiric course of this medication, is very popular in clinic setting. Really, the laryngoscopic examination has low specificity and pH monitoring is poorly sensitive, so the most accepted method in clinical practice to diagnose LPR is a trial of PPI therapy (8). As a diagnostic treatment, the PPI test is performed despite symptoms improving in suspected patients with reflux laryngitis. Altman suggested that empirical PPI therapy for a period of 1-2 months is a reasonable initial approach in patients with LPR symptoms (9). Patients unresponsive to PPI therapy have either non-reflux-related causes or may have a functional component to their symptoms. However, PPIs are overprescribed, expensive, and the safety profile may rise some uncertainty. In this regard, the prescriptive applicability is a mandatory aspect in the best practice. Therefore, even though pathognomonic signs and/or symptoms lack, LPR has become a primary diagnosis and resulted in patients experiencing a barrage of medications, specialty physician visits, diagnostic tests, and surgeries (10, 11). Thus, in the absence of a definitive diagnostic test, patient symptoms have become a primary method to identify those with LPR. Symptomatic differentiation of GERD and LPR should be possible if they indeed have discrete phenotypes (10). Therefore, patient-reported outcome (PRO) measures have become a principal means to diagnose LPR and monitor treatment outcomes.

However, if PRO measures are to be used to make patient-centered, symptom-based diagnosis and treatment decisions, they must be designed with appropriate methodological rigor. Use of poorly developed measures or those intended for a different application can have significant implications and lead to distorted, inaccurate, or equivocal findings (12, 13). While the ability to monitor change in LPR-symptoms or quality of life is an attribute most measures espouse, few instruments adequately demonstrated responsiveness to change. In this context, only two instruments met validity criterion: RSI (reflux symptoms index) and LPR-HRQL (LPR-health related quality of life) as recently evidenced (14, 15). So, patient-reported outcome measures are currently a principle method of diagnosing LPR and monitoring effectiveness of prescribed treatments. In particular, RSI seems to be very feasible and handy, as it is a self-completed questionnaire, consisting of 9 items (14). A score >13 is considered positive for LPR.

LPR treatment is based on two cornerstones: lifestyle modification and medical therapy. Modification of daily lifestyle is relevant in the LPR management. Avoidance of stimuli that may aggravate acid reflux, such as drinking alcohol, smoking, fatty foods, chocolate, acidic foods, spicy foods, and caffeine, is convenient. In addition, to raise the head of the bed during sleep, to avoid eating within 3 h of lying down, to perform adequate physical exercise, and to control the body weight are useful recommendations. Unfortunately, these measures are difficult to be complied and cannot be resolved. Accordingly, medical treatment remains the mainstay in LPR management. PPI and alginates are a common prescribed medication for LPR (17). Indeed PPI response rating is not completely satisfying in a large part of LPR patients, so alginates are commonly used (18). In this regard, a meta-analysis study evidenced that there was no difference between the PPI and placebo groups for LPR, whereas three trials exhibited statistically significant results (16).

A randomized controlled study showed that a liquid alginate suspension could achieve significant improvement in the symptom scores and clinical findings of LPR (19). Alginate has the characteristic of protection of the mucosal tissues from acid and non-acid reflux and displacement of acid pocket away from the oesophagus (20). Interestingly, alginate demonstrated non-inferiority to omeprazole and was as effective as omeprazole for symptomatic relief (21). Furthermore, adding alginate to a PPI can significantly relieve heartburn compared to

using a PPI alone, suggesting an additional benefit of alginate as add-on therapy in the management of refractory symptoms (22). However, these options could be used for long-term schedule, so alternatives should be considered.

As a new medical device has been introduced in the Italian market: Marial® (manufactured by Aurora, Milan, Italy) containing magnesium alginate and E-Gastryal®, an Italian survey explored the pragmatic approach of a group of otorhinolaryngologists in the LPR management. The aim of the current analysis was to evaluate the LPR patient's point of view during a therapy course using the RSI changes as an objective primary outcome.

MATERIAL AND METHODS

The current survey was conducted in 86 Otorhinolaryngological centers, distributed in all of Italy to assure a wide and complete national coverage. The otorhinolaryngologists were recruited to participate in the study. They endorsed to the Project RELIEF (Relieving LPR in Otolaryngology). They were asked to recruit all consecutive patients visited because of upper respiratory symptoms ascribable to a suspected LPR.

Patients were consecutively recruited during the specialist visit. The inclusion criteria were: to have a pragmatic diagnosis of LPR based on positive RSI and RFS scores (respectively >13 and >7) and/or suggestive history, both genders, and adulthood. Exclusion criteria were to have comorbidities able to interfere the evaluation of outcomes. As this survey was based on a real-world practice, doctors had the complete liberty of choosing the preferred medications on the basis of the best practice. Actually, three therapeutic options were prescribed: PPI as monotherapy, Marial® as monotherapy, and PPI plus add-on. The add-options included a miscellany of medication alternatives, including alginates, anti-acids, prokinetics, antiH2, and Marial®.

The treatment course lasted 4 weeks. Medications were taken following the specific indications. Patients were asked to weekly complete RSI questionnaire. Five RSI scores were available: at baseline, after 1, 2, 3, and 4 weeks. They were then collected in the specialist office without a new visit.

RSI was evaluated according to the protocol proposed by Belafsky (10). Items are analytically reported in another article published in the present Supplement.

Demographic and clinical characteristics were described using means with SDs for normally-distributed continuous data (i.e. age) or medians with lower and upper quartiles for not normally-distributed data (i.e. for RSI) or as absolute frequency and percentages for categorical data (i.e. frequency of treatments).

Difference in the median values of each continuous variable between before and after 4 weeks' treatment was evaluated with Wilcoxon signed rank test; when more than two groups were compared (i.e. total RSI weekly trend over time), Kruskal Wallis test, followed by Dunn's test, was used.

Statistical significance was set at $p < 0.05$, and the analyses were performed using GraphPad Prism software, GraphPad Software Inc, CA, USA.

RESULTS

Globally, 1.680 subjects [45.2% males, 54.8% females, 50.4 (14.7) years] were visited in the 86 Italian ORL centers and concluded the treatment course. All subjects completed the RSI questionnaire.

Fig. 1 shows the distribution of the different treatments prescribed by the Otolaryngologists: about 70% of patients were treated with Marial® alone, 27% with PPI plus add-on (almost always with Marial®), while only 7 patients (0.4%) were treated with PPI alone, and 36 patients (2.1%) were treated with a Miscellany option (including alginates, anti-acids, prokinetics, and antiH2).

Fig. 2A shows the median (IQR) RSI value in all patients at baseline and after 4 weeks (i.e. end of the therapy): RSI significantly diminished ($p=0.0001$). Fig. 2B shows the RSI trend over time (such as weekly): there was a significant diminution since the second week ($p<0.0001$).

Fig. 3 shows the trend of the total RSI values in patients treated with Marial® as monotherapy or with PPI plus add-on. Both treatments induced a significant reduction of the total RSI ($p<0.0001$ for both). In addition, Marial® induced a greater reduction of total RSI scores than PPI plus add- since the second week and until the end: $p<0.05$ at the second week; $p<0.01$ at the third week; and $p<0.05$

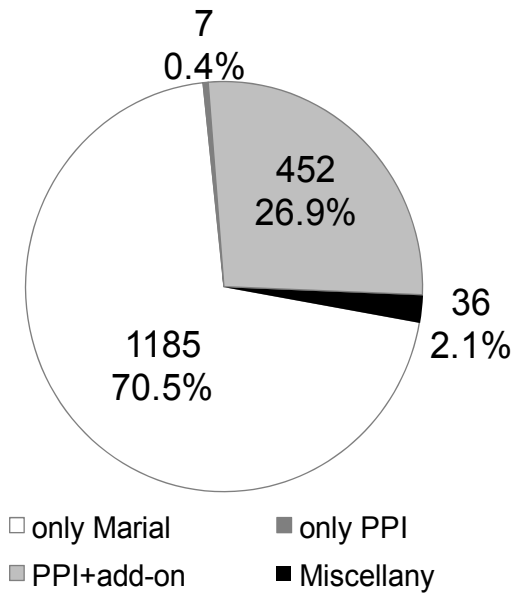

Fig. 1. *Distribution of the different treatments prescribed by the Otolaryngologists.*

at the fourth week. Noteworthy, both treatments reduced RSI scores below the cut-off (i.e. <13) since the second week. Moreover, Marial® induced a 74% reduction of RSI score, whereas PPI plus add-on a 70% reduction of RSI score ($p<0.0001$).

Fig. 4 reports the changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with Marial®. All symptoms significantly diminished ($p=0.0001$ for all symptoms). Noteworthy to observe is that some symptoms disappeared, such as heartburning and dyspnoea.

Fig. 5 shows the changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with PPI plus add-on. All symptoms significantly diminished ($p=0.0001$ for all symptoms). Noteworthy, some symptoms disappeared, such as heartburning difficulty to swallowing, and dyspnoea.

Fig. 6 shows the percentages of RSI reduction for each single symptom before and after a 4 week-

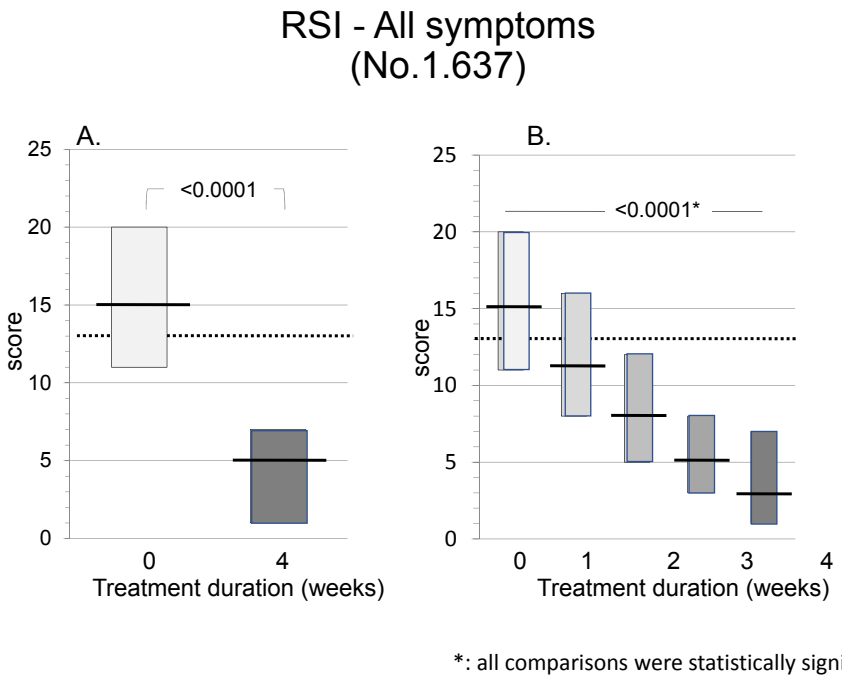

Fig. 2. *Total RSI value in all patients at baseline and after 4 weeks (i.e. end of the therapy) (**panel A**) and total RSI weekly trend over time (**panel B**).*

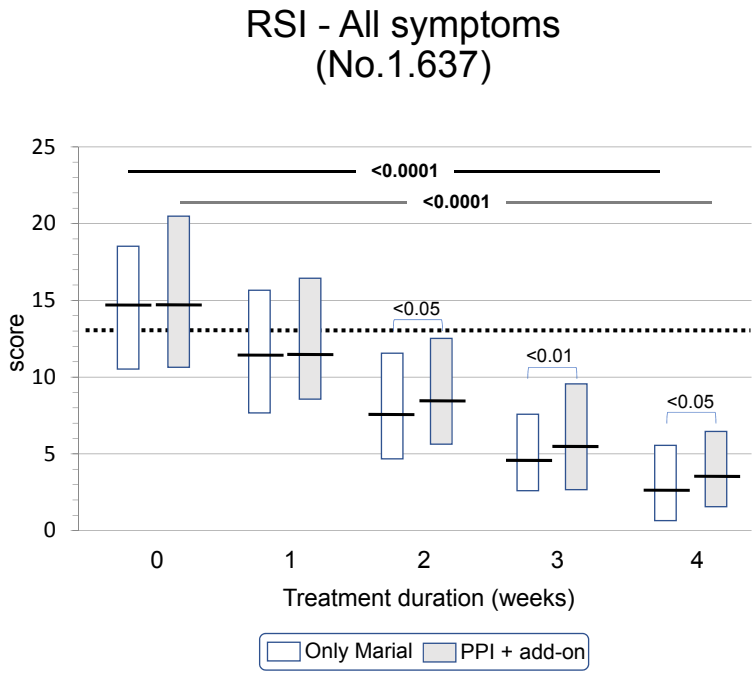

Fig. 3. *Trend of the total RSI values in patients treated with Marial® as monotherapy and with PPI plus add-on.*

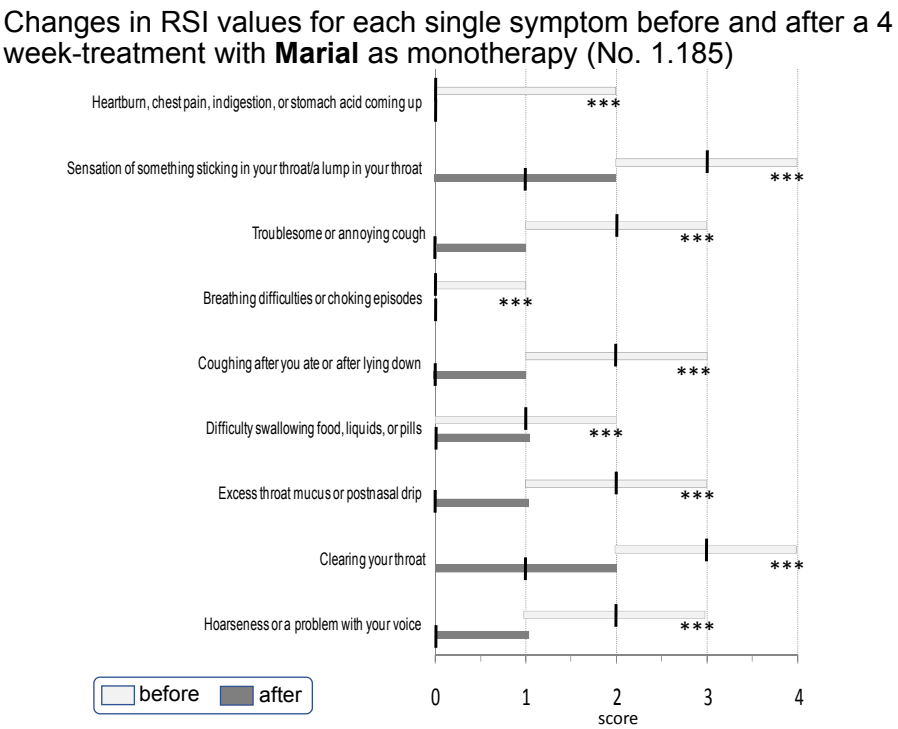

Fig. 4. *Changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with Marial® alone.*

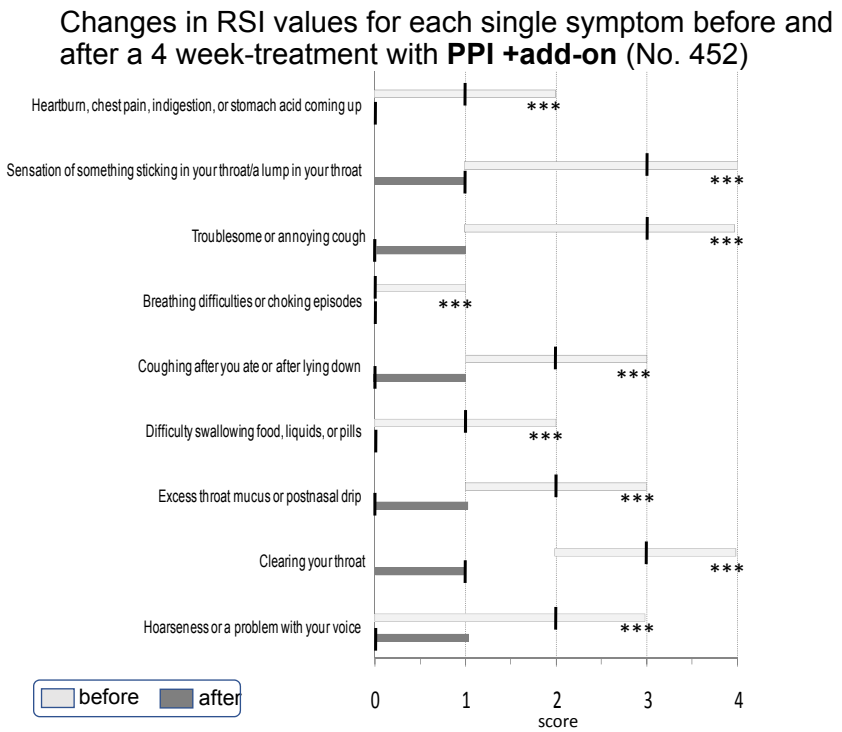

Fig. 5. *Changes in RSI scores for each single symptom evaluated before and after the 4-week treatment with PPI plus add-on.*

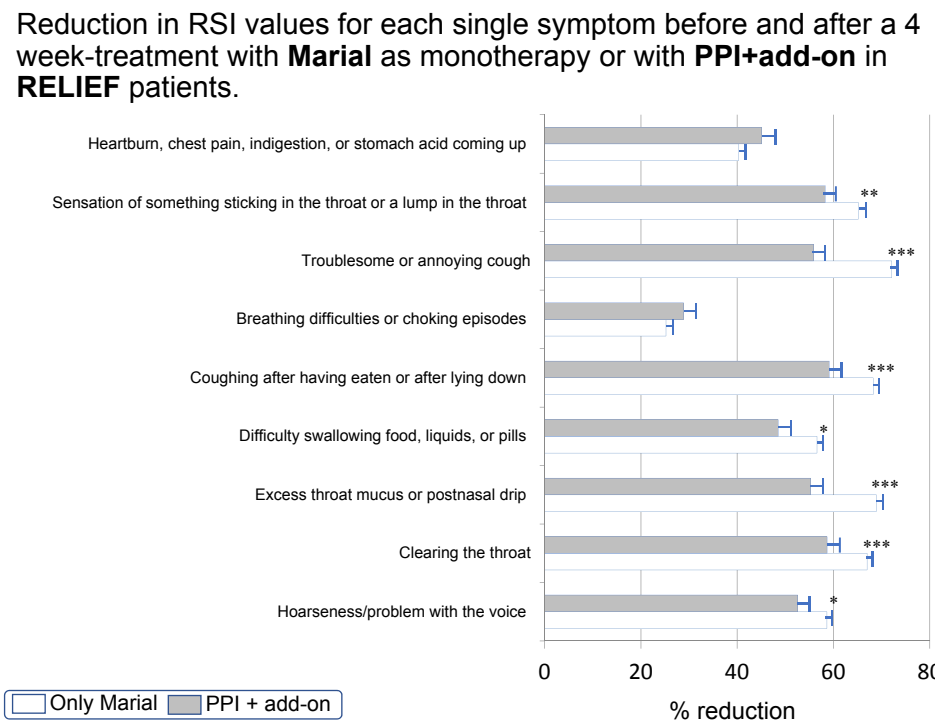

Fig. 6. *Percentages of RSI reduction for each single symptom in patients treated with Marial® as monotherapy and with PPI plus add-on.*

treatment with Marial® as monotherapy or with PPI in add-on. As compared to PPI in add-on, Marial® as monotherapy induced a statistically significant reduction in each single symptoms with the exception of breathing difficulties or choking episodes and heartburn, chest pain, indigestion, or stomach acid coming up.

DISCUSSION

Laryngopharyngeal Reflux constitutes a common disease, frequently underdiagnosed and mistreated. The diagnosis is based on patient's history and on a clinical ground. Validated method to assess the severity of signs and symptoms are very fruitful in clinical practice. In particular, the point of view of the LPR patient gained recognized respect and regard. The possibility of carefully measuring symptom severity by validated methods has allowed to obtain useful outcomes in clinical practice. In this regard, RSI is a validated psychometric questionnaire that is recommended both for LPR diagnostic work-up and evaluation of changes after treatments.

The launch in the Italian market of a new medical device (Marial®) represented an opportunity for LPR treatment. The novelty is the specific indication for LPR. Marial® is a combination of two substances: magnesium alginate and E-Gastryal® (a complex of phyto-polymers containing hyaluronic acid, hydrolysed keratin, Tara gum, and Xantana gum).

The present Italian survey aimed to evaluate the LPR management in clinical practice, mainly concerning the otolaryngologist clinic setting. In particular, the present analysis considered the LPR patient's perception of treatment changes using a validated method, such as the RSI score (14). Patients completed RSI questionnaires weekly during a 4-week treatment course. Therapeutic options were Marial® as monotherapy, or PPI plus add-on.

Globally, a significant reduction of symptom severity, measured by RSI, was achieved after both treatments. Interestingly, significant different change behaviour was evident among symptoms.

In particular, some symptoms disappeared, such as heartburning and dyspnoea. When comparing the two therapeutic options, it was demonstrated that Marial® induced a greater reduction of symptoms than PPI plus add-on since the second week. In particular, Marial® induced an 74% reduced of the RSI score, whereas PPI plus add-on gave a 70% reduction.

Even though the present survey should not be considered as a conventional trial, it permits to deduce some speculations. Marial® treatment was effective and rapid in relieving LPR complaints. Surprisingly, Marial® was more effective of PPI plus add-on. Another interesting issue is the rapidity of the therapeutic effect: since the second week.

Of course, the lack of a randomization, a double-blind design, a follow-up, and of a placebo group reduce the evidence-based scientific value of the current experience. Therefore, further studies should be conducted to address these unmet needs. However, the real-world setting, the large number of the recruited patients, and the use of a validate and consolidated instrument, i.e. the RSI questionnaire, have to be adequately considered. In particular, RSI assessment is clinically relevant as it expresses the point of view of the patients. This issue is very important as failing gold standard diagnostic criteria, the patient's perception of symptom severity change has a pragmatic value.

In conclusion, the present survey reported that a new medical device (Marial®) may be considered a valid option for the treatment of LPR.

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CORRELATION BETWEEN THE REFLUX FINDING SCORE AND THE REFLUX SYMPTOM INDEX IN PATIENTS WITH LARYNGOPHARYNGEAL REFLUX

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LaryngoPharyngeal Reflux (LPR) is characterized by symptoms, signs, and/or tissue damage resulting from the aggression of the gastrointestinal contents in the upper airways. The Reflux Finding Score (RFS) assesses the laryngeal signs through laryngoscopy. The Reflux Symptom Index (RSI) scores the LPR symptoms. The objective of this real-world study was to compare RFS with RSI in a cohort of Italian LPR patients. Globally, 3932 patients with LPR were evaluated and RFS and RSI were assessed in all subjects. A moderate correlation was found between RSI and RFS (r=0.484, p<0.0001). In conclusion, the RSI and RFS can easily be included in the LPR work-up as objective and consistent parameters, with low cost and high practicality. Based on these clinical outcomes, the specialist can easily use these tests in clinical practice.

Gastroesophageal Reflux Disease is a polymorphic disorder presenting variable symptoms associated with esophageal and/or extra-esophageal damage. Extraesophageal symptoms were reported by 58% of patients with classic symptoms, such as heartburn and regurgitation, in these patients, there was a worsening of quality of life score (1). Koufman coined the term LaryngoPharyngeal Reflux (LPR) for defining the symptoms, the signs, and/or the tissue damage resulting from the aggression of the acid gastric contents to the upper airways (2). Two main pathogenic mechanisms have beenhypothesized: a local physical-chemical irritation on the laryngopharyngeal mucosa or a vagal reflex stimulation induced by the refluxate (3). However, gastroenterologists and otolaryngologists do not agree about the definition and the diagnosis of LPR.

In this regard, Belafsky proposed a scoring of the signs observed during the laryngoscopy: the Reflux Finding Score (RFS) to make objective the diagnosis (4). In addition, Belafsky also proposed the Reflux Symptom Index (RSI), a self-administered questionnaire to score the LPR symptoms (5). Therefore, RFS and RSI may be very useful tools in the diagnostic work-up of LPR as they allow to quantify severity of clinical features and so suggest LPR diagnosis. In fact, RFS value >7 and RSI score

Key words: gastric reflux, GERD, laryngo-pharyngeal reflux, Marial®

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>13 may support LPR diagnosis. Recently, a study compared the Reflux Finding Score (RFS) with the Reflux Symptom Index (RSI) in the otolaryngological practice (6). These authors concluded that RSI and RFS can easily be included in otolaryngological routine as objective parameters, with low cost and high practicality. However, the statistical analysis did not consider the evaluation of a real relationship between the two tests.

The present study aimed to correlate RFS with RSI in a wide cohort of Italian LPR patients evaluated in a real-world setting, such as otolaryngological clinics.

MATERIALS AND METHODS

Globally, 3.932 patients [53.2% women and 46.8% men, 50.2 (14.5) mean age] were consecutively visited and enrolled in 86 otolaryngological Italian centers. The inclusion criteria were LPR diagnosis and both genders. Exclusion criteria were other digestive disorder and/or diseases able to interfere with the findings interpretation.

Patients were visited and completed the RSI questionnaire. Laryngoscopy was performed in all patients and so RFS was calculated.

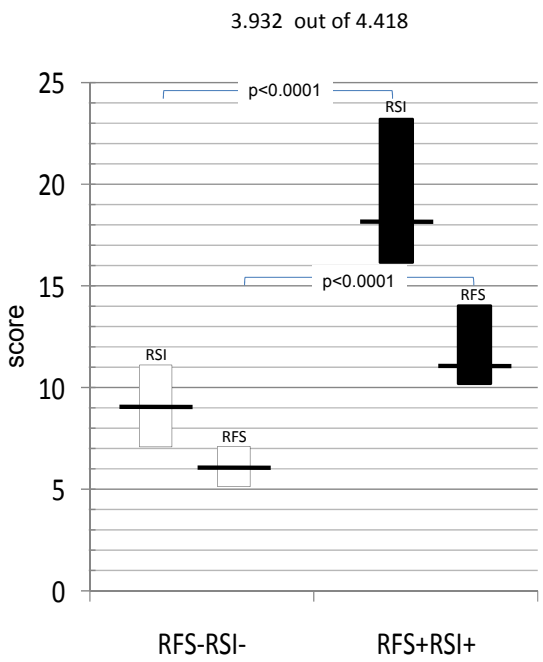

Fig. 1. *RFS and RSI values in patients with positive scores of RFS and RSI (RFS+RSI+) and in patients with negative scores of RFS and RSI (RFS-RSI-).*

RFS was evaluated according to the protocol proposed by Belafsky (4). A score >7 was considered positive, such as able to confirm LPR diagnosis.

RSI was evaluated according to the protocol proposed by Belafsky (5). A score >13 was considered positive, such as able to confirm LPR diagnosis.

Demographic and clinical characteristics were described using means with SDs for normally-distributed continuous data (i.e. age) or medians with lower and upper quartiles for not normally-distributed data (i.e. for RSI or RFS).

Correlation between the RSI score and the RFS score was evaluated with Spearman rank-order correlation coefficient. Statistical significance was set at $p<0.05$, and the analyses were performed using GraphPad Prism software, GraphPad Software Inc, CA, USA.

RESULTS

Globally, 3.932 patients were visited; 2.234 patients were RFS+RSI+ and 608 were RFS-RSI-. Fig. 1 shows the median RFS and RSI values in the 2 subgroups: there was a significant difference both concerning RFS and RSI ($p<0.0001$ for both).

Fig. 2 shows the relationship between RFS and RSI in the whole population: a moderate correlation was found between RSI and RFS ($r=0.484$, $p<0.0001$).

On the contrary, a lack in the association between RSI and RFS was found when RSI+RFS+ patients and RSI-RFS- patients were analyzed separately (data not shown).

DISCUSSION

Gastroesophageal reflux disease (GERD) is a clinical definition that refers to an excessive gastric reflux that usually causes tissue damage and/or clinical symptoms (6). However, LPR defines signs, symptoms, and/or laryngopharyngeal injury resulting from the reflux of gastroduodenal contents into the upper airways (2). The previous Brazilian study, comparing RFS with RSI, reported: a higher LPR prevalence in women (69%), and dry cough as the most common symptoms (6). These outcomes were partially inconsistent with

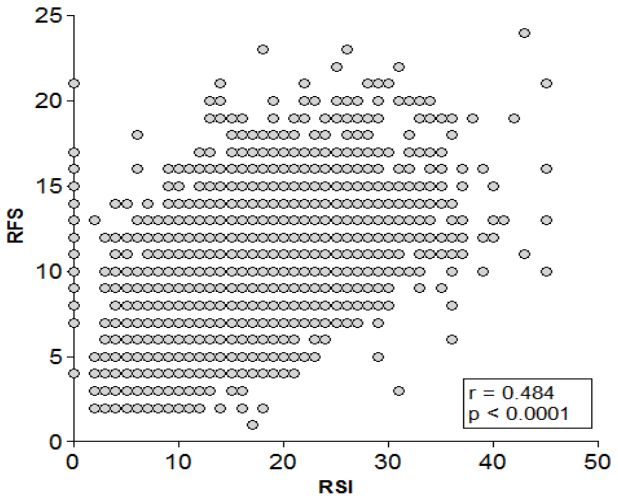

Fig. 2. *Correlation between the RSI score and the RFS score in the whole population (No. 3.932).*

literature (7-11). Therefore, the present study was performed to compare RSI with RFS in a wide cohort of LPR patients enrolled in a real-world setting, such as 86 Italian otolaryngological clinics. The present study reported that there was a significant and weak-moderate relationship between RFS values and RSI scores, considering the whole evaluated population of LPR patients. On the contrary, subdividing patients in 2 subgroups, such as patients with both tests positive or both tests negative, the significance disappeared.

This positive outcome underlines the relevance and the consistency of these diagnostic questionnaires as clinically relevant tools in the diagnostic work-up in patients with suspected LPR. RSI is a simple self-administered questionnaire that requires very few minutes to be completed. RFS is based on the scoring of signs evaluated during a routine laryngoscopy. As laryngoscopy is at present a routine exam performed during the otolaryngological visit in clinical practice.

On the other hand, this study has an important limitation: the lack of other diagnostic tests. However, the strength of the current study is the real-world study design and the very large number of enrolled patients.

In conclusion, the RSI and RFS tests can easily be included in the LPR work-up as objective parameters, with low cost and high practicality. Based on these clinical outcomes, the specialist can easily use them in clinical practice.

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GASTRIC REFLUX: COMPARISON BETWEEN THE GASTROENTEROLOGIST AND THE OTORHINOLARYNGOLOGIST'S APPROACH. PRAGMATIC CONCLUSIVE REMARKS

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Conclusions:

Gastroesophageal reflux (GER) is a normal physiological process that usually happens after eating in healthy infants, children, young people and adults. In contrast, gastroesophageal reflux disease (GERD) occurs when the effect of GER leads to symptoms severe enough to merit medical treatment. In clinical practice, it is difficult to differentiate between GER and GERD, and health professionals and families use the terms interchangeably alike. There is no simple, reliable and accurate diagnostic test to confirm whether the condition is GER or GERD, and this in turn affects research and clinical decisions (1-6). Furthermore, the term GERD covers a number of specific conditions that have different effects and present in different ways. This makes it difficult to identify the person who genuinely has GERD, and to estimate the real prevalence and burden of the problem.

Nevertheless, regardless of the definition used, GERD affects many subjects, who commonly seek advice from primary, secondary or tertiary care. As a result, it constitutes a major health burden for the Health Service. Moreover, if gastric reflux moves more proximally into the laryngopharynx, it is defined laryngopharyngeal reflux (LPR). LPR should be considered as part of extraesophageal reflux (EER), a reflux involving structures other than, or in addition to, the oesophagus, and airway reflux involving proximal gastric reflux into the airways. LPR contributes to several otorhinolaryngologic symptoms and inflammatory disorders, and probably also to neoplastic diseases of the laryngopharynx, and seems to be also as common in children and infants as adults.

From a diagnostic point of view, GERD and LPR diagnosis may be performed on a clinical ground as there is no gold-standard diagnostic tool. In this regard, some questionnaires may very fruitful in clinical practice: Reflux Finding Score (RFS) based on signs viewed by laryngoscopy, Reflux Score Index (RSI) based on reflux symptoms, and GERD Impact Scale (GIS) based on frequency of symptoms.

From a management point of view, the guidelines suggest to give advice about GER and reassure patients and caregivers. Patients with dyspepsia with mild-moderate symptoms and without severe complications, such as bleeding, painful complaints, vomiting, could be treated with empirical full-dose PPI therapy for 4 weeks. Patients with GERD could be treated with a full-dose PPI for 4 or 8 weeks. If symptoms recur after initial treatment, a PPI could be offered at the lowest dose possible to control symptoms. In addition, it is recommended to encourage people who need long-term management of dyspepsia symptoms to reduce their use of prescribed medication stepwise: by using the effective lowest dose, by trying 'as-needed' use

Key words: gastric reflux, GERD, laryngo-pharyngeal reflux, Marial®

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

when appropriate, and by returning to self-treatment with antacid and/or alginate therapy (unless there is an underlying condition or co-medication that needs continuing treatment). It is also necessary to advise people that it may be appropriate for them to return to self-treatment with antacid and/or alginate therapy (either prescribed or purchased over-the-counter and taken as needed). Finally, it is important to avoid long-term, frequent dose and continuous antacid therapy (it only relieves symptoms in the short term rather than preventing them).

On the basis of these considerations, proposed by guidelines, alginates may be considered as a valid and reasonable therapeutic option. 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, keratin, 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.

Therefore, two large surveys were conducted in Italy: RELIEF, involving 86 otolaryngologists, and EMERGE, involving 56 gastroenterologists. The aims of these surveys were: 1): to define clinical characteristics, including previous treatment, of the patients referred to consultation;

2): to evaluate the reliability of RFS, GIS, and RSI questionnaires in real-world settings, such as specialist office;

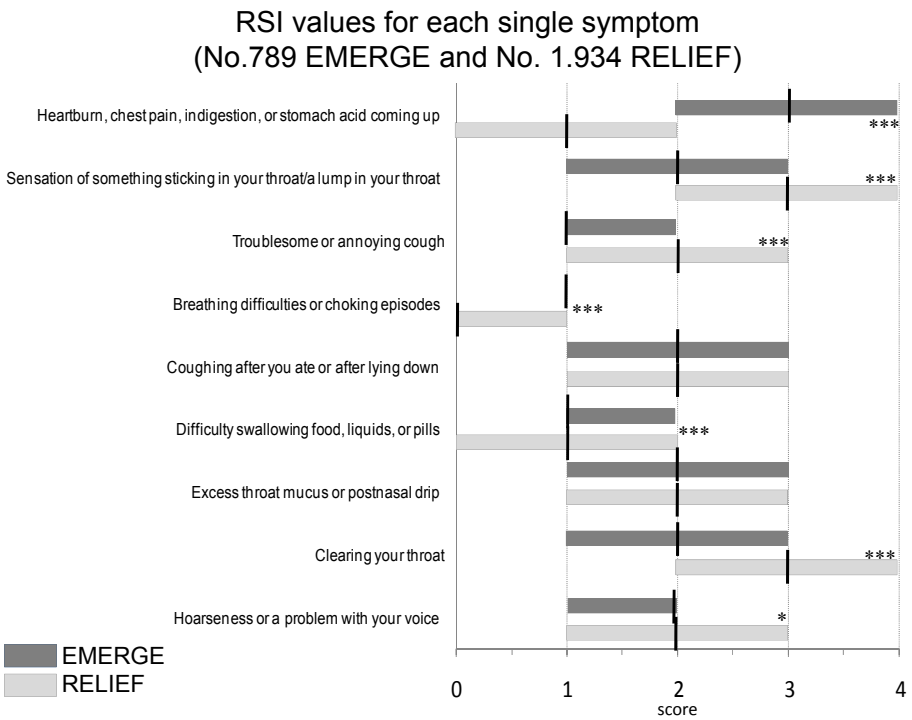

Fig. 1. *Reflux symptom index (RSI) as median values for each single symptom in the EMERGE (No. 789) and in the RELIEF population (No. 1.934). Scores are reported as medians (**bars**) with lower and upper quartiles (**boxes**).*

3): to investigate the patients' perception of efficacy of the prescribed therapy, based on the best practice and considering also the new medical device.

In the current supplement, the outcomes of these surveys are presented and discussed. Now, we would draw the conclusive remarks from a pragmatic point of view. Therefore we compared the most relevant outcomes obtained by the two surveys.

First, we compared RSI questionnaires: at baseline, RSI questionnaire was filled by 1,934 RELIEF patients and by 789 EMERGE patients. Globally, 594 (75.3%) EMERGE patients and 1250 (64.6%) RELIEF patients had positive RSI score. RSI values for each single symptom are analytically reported in Fig.1. The symptoms with the highest score were: heartburning, sensation of something sticking in the throat or a lump in the throat, and clearing throat, whereas breathing difficulties or choking episodes had the lowest score. The total score was 16 (14-20) in the EMERGE patients was significantly higher than in the RELIEFE patients: 16 (12-20) ($p<0.001$; data not shown).

Interestingly, RELIEF patients had significantly higher scores for some symptoms, including lump sensation, cough, dyspnea, hoarseness, and throat clearing, whereas EMERGE patients had higher scores for heartburn and difficult swallowing and the clinical features were really different in the two populations, such as GERD and LPR patients.

Considering the previous treatments, the frequency of past/current treatments in the EMERGE group (Fig. 2A) was significantly higher than in RELIEF group (Fig. 2B) patients ($p<0.0001$): this outcome underlines the more intense recourse to medical therapy in GERD patients than in LPR patients.

Analyzing the treatment options, Fig. 3 shows the distribution of different types of treatments prescribed in the past (panel A, C) or currently used (panel B, D): monotherapy with PPI, PPI in add-on, and Miscellany in EMERGE (panel A, B) and RELIEF (panel C, D) patients. LPR patients were more frequently treated with PPI as monotherapy and with miscellany treatments, whereas GERD patients use more commonly PPI plus add-on, even though PPI alone are the first-choice therapy also in GERD. Considering the distribution of the new prescribed treatments (i.e. prescriptions made during the visits) and specifically of Marial® as monotherapy, PPI as

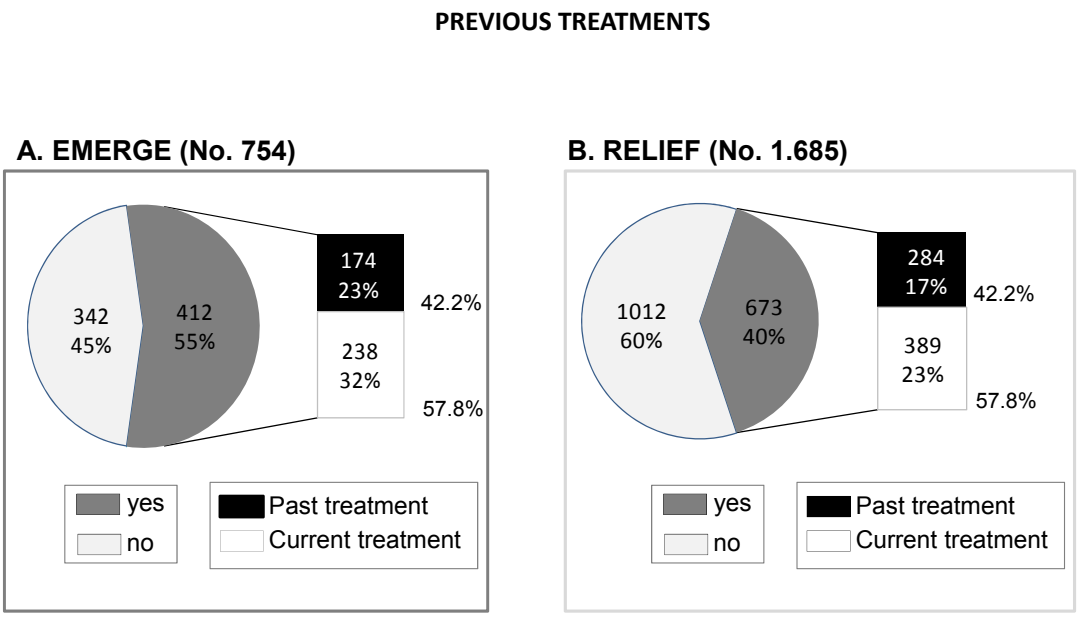

Fig. 2. *Distribution of the EMERGE (**panel A**) or RELIEF (**Panel B**) patients according to the treatments: past, current or never.*

monotherapy or PPI in add-on, there was difference in EMERGE (Fig. 4A) and in RELIEF (Fig. 4B) patients ($p<0.0001$): LPR patients were preferentially treated with Marial® alone, whereas GERD patients were treated essentially with PPI plus add-on.

Comparing the patients' perception of treatment efficacy, reduction in RSI values for each single symptom before and after a 4 week-treatment with Marial® alone or with PPI in add-on in EMERGE and RELIEF patients are reported in Fig. 5 and 6. Marial® alone treatment induced a statistically significant higher reduction in each single symptom in RELIEF patients than in EMERGE patients, with the exception of heartburn, chest pain, indigestion,

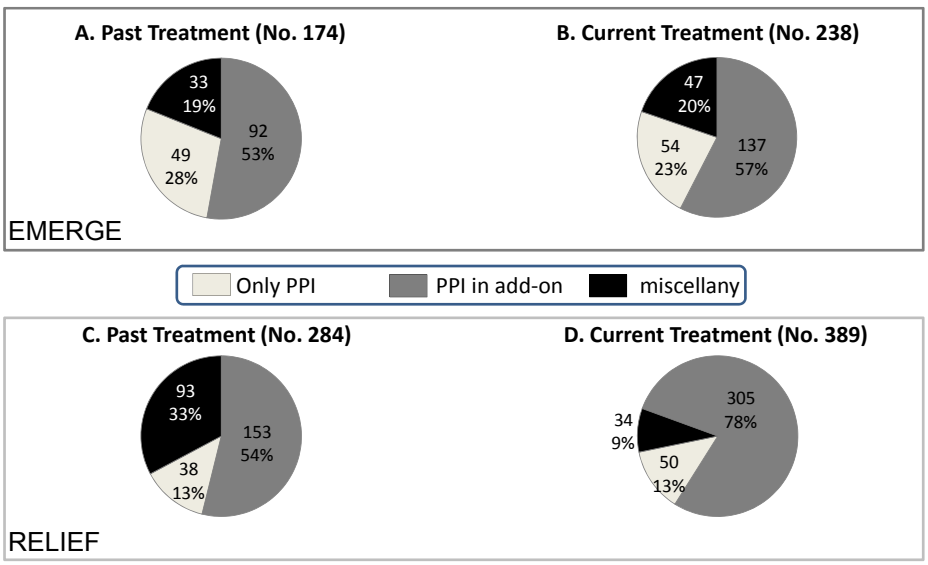

Fig. 3. *Distribution of different types of treatments prescribed in the past (**panel A, C**) or currently used (**panel B, D**): monotherapy with PPI, PPI in add-on, and Miscellany in EMERGE (**panel A, B**) and RELIEF (**panel C, D**) patients.*

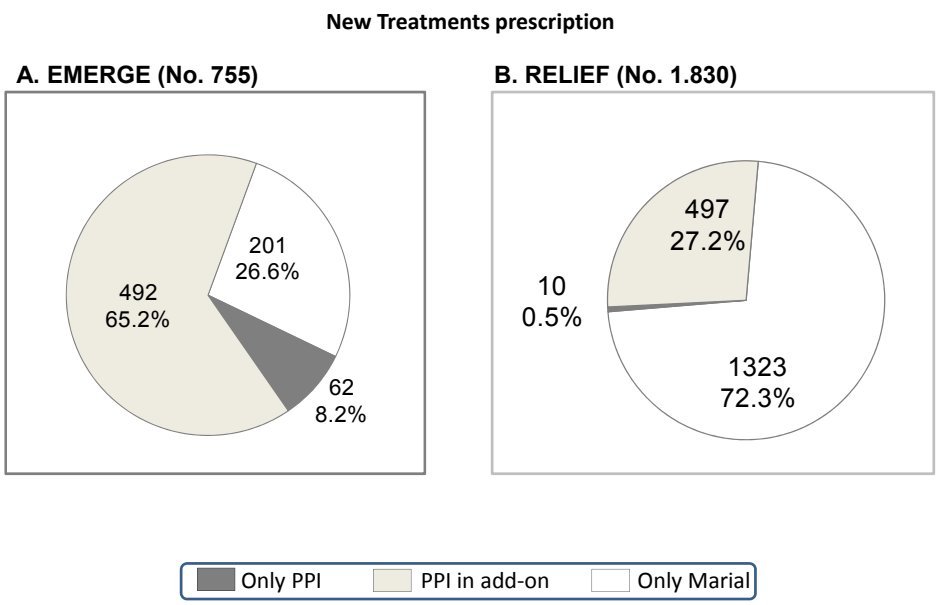

Fig. 4. *Distribution of the Marial® as monotherapy, PPI as monotherapy or PPI in add-on in new prescribed treatments (i.e. prescriptionduring the visit) in EMERGE (**panel A**) and RELIEF (**panel B**) patients.*

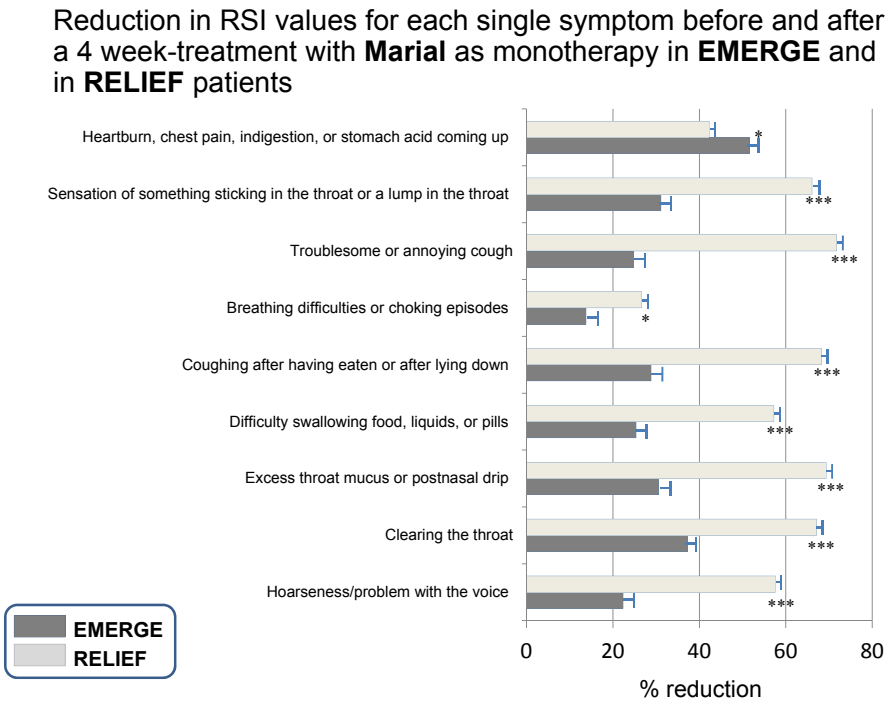

Fig. 5. *Reduction in RSI values for each single symptom before and after a 4 week-treatment with Marial® as monotherapy in EMERGE and in RELIEF patients.*

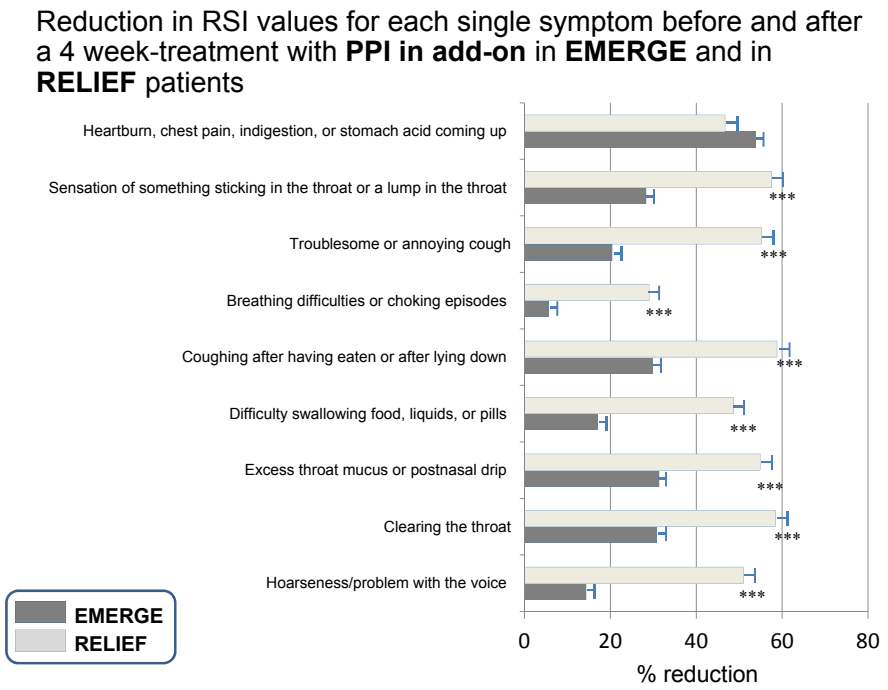

Fig. 6. *Reduction in RSI values for each single symptom before and after a 4 week-treatment with PPI+add-on in EMERGE and in RELIEF patients.*

or stomach acid coming up (Fig. 5). Similar results were obtained evaluating the reduction in RSI values in patients treated with PPI in add-on that was able to determine a higher statistically significant decrease in RELIEF than in EMERGE patients in each single symptom, with the exception of heartburn, chest pain, indigestion, or stomach acid coming up (Fig. 6).

In conclusion, these two surveys provided some interesting outcomes:

i): diagnostic questionnaires (RSI, RFS, and GIS) are reliable and useful both during the visit and to orient the treatment decision;

ii): GERD and LPR present different clinical features;

iii): as consequence the treatments (both previous and actual) are different;

iv): the introduction of Marial® significantly affected the otolaryngologist approach and partially the gastroenterologist orientation;

v): Marial® was effective both in LPR and GERD patients;

vi): Marial® showed more effectiveness than conventional therapy (PPI plus add-on);

vii): LPR patients were more responsive to medical treatments than GERD patients.

Therefore, these outcomes may give a pragmatic usefulness to both otolaryngologists and gastroenterologists in clinical practice.

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SALSO-BROMO-IODINE THERMAL WATER: A NONPHARMACOLOGICAL ALTERNATIVE TREATMENT FOR POSTNASAL DRIP-RELATED COUGH IN CHILDREN WITH UPPER RESPIRATORY TRACT INFECTIONS

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Postnasal drip (PND)-related cough is a very common symptom in patients with upper respiratory tract infections (URTIs). At present, there is not a standard treatment for postnasal drip and postnasal drip-related cough. The aim of this pilot study was to evaluate the efficacy of a specific salso-bromo-iodine thermal water containing hyaluronic acid and grapefruit seed extract (SBI-H-GSE) comparing it with a normal saline solution in children with URTIs who refer PND-related symptoms. The study was randomized, single-blind, and controlled. Study group (75 children) was treated with SBI-H-GSE and control group (65 children) was treated with a normal saline solution; both compounds were administered by nasal nebulization with Rinowash nasal douche twice/day for 10 days a month for 3 consecutive months. Parent Cough-Specific Quality of Life questionnaire (PC-QOL) average score, the prevalence of symptoms and signs related to post-nasal drip, nasal mucociliary transport time (NMTT), duration and number of URTI episodes, antibiotic usage and days of absence from school were evaluated at baseline and after treatment. SBI-H-GSE therapy shows better and statistically significant trend after treatment when compared to control group for PC-QOL average score (p=0.011), NMTT (p=0.047), symptoms and signs related to post-nasal drip (all p<0.005, except for the cobblestone appearance of the mucosa), duration (in days) with URTI symptoms (p=0.023) and a usage of antibiotic therapy (p=0.011). The current randomized-controlled pilot study demonstrated that SBI-H-GSE solution was effective in the treatment of children with URTIs who refer PND-related symptoms.

Postnasal drip (PND) was first described by Dobell in 1866, since then several studies support this century-old argument that increases in nasal secretions running down posteriorly into the larynx and pharynx is the cause of an irritation and chronic cough (1). PND is one of the most common causes of chronic cough in childhood, although, the mechanism on how the cough reflex is induced has not been established and it is still debated (2). PND may have multiple causes in the child as allergic rhinitis, enlarged adenoids, sinusitis, gastroesophageal reflux, nasal polyps, anatomical anomalies, mucociliary dysfunction and immunodeficiencies (3).

It is often described as a chronic problem related to repeated episodes of upper respiratory tract infections (URTIs) that leaves children with a persistent condition of catarrh and PND, probably due to some change in mucociliary clearance causing accumulation of mucus in the postnasal space (3).

Current treatment recommendations of PND

Key words: Salso-bromo-iodine thermal water, isotonic saline, postnasal drip

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continue to be based on assumption that it is a sinonasal disease process (1). Suggested therapies include nasal washing, especially in case of sinusitis, with a nasal solution which promotes mucociliary clearance and removes the excess of nasal mucus (4), antihistamines, decongestants, antibiotics, topical nasal steroids and bacteriotherapy (5-7).

The salso-bromo-iodine thermal waters are very well known and appreciated for their positive effects in the treatment of URTIs, indeed it has been demonstrated that the use of salso-bromo-iodine thermal waters enhances mucociliary clearance, as well as improving the cough due to PND (8).

The aim of this pilot study was to assess the efficacy of a specific salso-bromo-iodine thermal water containing hyaluronic acid and grapefruit seed extract (SBI-H-GSE) comparing it with a normal saline solution in children with URTIs who refer PND-related symptoms.

MATERIAL AND METHODS

A prospective, single-blind, randomized, open-label, placebo-controlled clinical trial with two parallel groups was conducted at the ENT Unit, Acireale Hospital, between October 2016 and December 2017. The study was approved by the Institutional Review Board Hospital and it was conducted in accordance with the ethical principles out-lined in the Declaration of Helsinki. The patients were children, aged between 6 and 14 years, with URTIs. The definition used for URTI episodes required for study eligibility was defined by the presence of at least two of the following: purulent nasal discharge, cough, pharyngo-tonsillar erythema or exudates, temperature ≥38.5°C and otalgia (earache), or prescription of an antibiotic for URTI, occurring after an asymptomatic period of at least 1 week without antibiotics. Exclusion criteria were occurrence of infection of the lower respiratory tract (bronchitis, pneumonia) at the enrollment visit. Further exclusion criteria were the presence of allergic rhinitis, congenital immunodeficiencies and bronchopulmonary disease, cystic fibrosis, previous adenoidectomy and/or tonsillectomy, recent immunosuppressive or immunostimulant therapy, or corticosteroids.

Children fulfilling the inclusion/exclusion criteria and whose parents or guardians gave their informed consent, were randomly assigned by a biostatistician, not involved in the study and using a computer-assisted random sequence generator, to an intervention group treated with SBI-H-GSE watery solution, (Broncalt, Aurora Biofarma Srl, Milano) or to a control group who received the administration of normal 0.9% sodium chloride saline solution. Both compounds were administered by a micronized nasal douche (Rhinowash, Air Liquide Medical Systems Italy S.p.A., Brescia, Italy) twice/day for 10 days a month for 3 consecutive months.

All the children were visited at baseline and at the end of the treatment. During every visit, the following parameters were checked: the impact of cough on Quality-of-life (QOL) assessed by a disease-specific parent-proxy questionnaire, the Parent Cough-Specific Quality of Life questionnaire (PC-QOL) and a 27-item questionnaire that assesses parents' feelings and worries related to their child's cough. It uses a 7-point Likert-type scale, with lower scores reflecting worse QOL (9), prevalence of symptoms and signs related to PND as sensation of having something drip down on to the throat, the need to frequently clear the throat, cobblestone appearance of the nasopharyngeal mucosa, mucus secretion in the oropharynx and nasal discharge (5, 10), determination of nasal mucociliar transport time (NMTT) assessed with the saccharine transit test using a technique described previously (11). Duration and number of URTI episodes, antibiotic usage (in times) and days of absence from school were also evaluated. All these parameters were assessed by an otolaryngologist not involved in the study.

Data are reported as means ± SD for continuous variables, while categorical variables were expressed as frequencies and percentages. Student *t*-tests were used to compare the means for continuous data. If the normality test failed, the Mann-Whitney U test was applied. For categorical data, the chi-square test was used. All statistical tests were performed with the MedCalc Statistical Software, v. 9.2.1.0 (MedCalc Software, Belgium) and p values of less than 0.05 were regarded as statistically significant.

RESULTS

Of the 145 children who met the inclusion criteria and consented to take part in this study, 140 subjects completed the treatment period. Five subjects

(3.4%), 3 belonging to the SBI-H-GSE group and 2 to the control group, were lost until the end of the study, so a total of 140 patients (80 male, mean age 11.4±2.5 years) were included in the final analysis.

Patients of the two study groups were similar in terms of age, gender duration and number of URTI episodes. The characteristics of the study participants are summarized in Table I.

The PC-QOL questionnaire average score was significantly higher after treatment both in the SBI-H-GSE group and control group when compared to the baseline values, indicating a better QOL in the two study groups, although a better improvement was observed in the SBI-H-GSE group, as revealed by a higher reduction in the mean score when compared to post-treatment control group values (5.4±1.2 vs 4.4±1.1, respectively, p=0.011). A significant improvement in NMTT (in minutes) after 3 months of treatment was observed in both study groups, however, a significant difference in favor of SBI-H-GSE group was observed when post-treatment values were compared between groups (p=0.047) (Table II).

The prevalence of all symptoms and signs related to PND decreased from baseline to after treatment for all groups. However, when compared with the control group, it was observed that the SBI-H-GSE group experienced a significantly lower prevalence of sensation of having something drip down on to the throat (p=0.002), need to frequently clear the throat (p=0.010), mucus secretion in the oropharynx (p=0.027) and nasal discharge (p=0.033) (Table III).

When URTIs episodes were taken into account, a significant difference in days with URTI symptoms and ancillary therapy usage was observed between the 2 groups. Further analysis showed that a significantly lower duration (in days) with URTI symptoms were observed in SBI-H-GSE group after treatment period as compared to controls (10.4±2.7 vs 14.8±3.1, respectively, p=0.023), as well as, a lower usage of antibiotic therapy (2.5±0.3 vs 4.8±0.4, respectively, p=0.011). On the contrary, no significant difference was observed for the number of URTI episodes or absence from school, although the latter is significantly lower for both groups when compared to baseline and after treatment results, but it did not reach statistical significance when compared between the two groups (p=0.127) (Table IV).

DISCUSSION

PND-related cough is a very common symptom in patients with URTIs. Subjects often describe a sensation of "fluid dripping" or "something being present in the throat" often associated with cough and throat clearing (12).

The upper airway infections cause increased volume of secretions which is due to increased plasma exudate caused by increased capillary permeability for the inflammation mechanism (13) and some change in mucociliary clearance that causes accumulation of mucus in the postnasal space and consequently into the posterior nasopharynx/oropharynx resulting in PND (2). Alternative explanations include the possibility that it is not an increased volume of nasal secretions which result in the sensation of PND but an alteration in the viscosity of the nasal secretions or it may be a symptom associated with airway inflammation (12, 14).

At present, there is not a standard treatment for postnasal drip and postnasal drip-related cough because objective diagnostic tests are missing and its symptoms are variable (1), so it is asserted that the treatment of the underlying condition may help to resolve the PND (2).

In several mucous-secretory disorders, as URTIs are, the effect of salso-bromo-iodine thermal waters may represent a valid alternative approach, being very well known and appreciated their positive effects on acute and chronic inflammatory respiratory diseases due to anti-catarrhal, anti-inflammatory, mucociliary transport normalizer, antiseptic and immunostimulant action (increase of total serum IgA and reduction of total serum IgE) (8, 15).

Our results confirm that salso-bromo-iodine thermal waters allow the improvement of mucociliary function, as confirmed by a significant reduction of mean mucociliary transport time in favor of SBI-H-GSE group when compared to normal saline solution. Furthermore, both a better improvement on PC-QOL

Table I. *Demographics and URTIs characteristics of the two study groups.*

Characteristics	SBI-H-GSE group N=75	Control group N=65	Overall N=140	*p-value*
Age, in years				
Mean±SD	11.8±2.6	10.9±2.3	11.4±2.5	0.347
Median	10	10	10	-
Range	6-14	6-14	6-14	-
Gender, n(%)				
Male	44(58.7)	36(55.4)	80(57.1)	0.218
Female	31(41.3)	29(44.6)	60(42.9)	
Days with URTI symptoms, Mean±SD	15.6±4.8	15.2±3.5	15.4±4.2	0.616
Episodes of URTI, Mean±SD	2.7±0.5	2.5±0.6	2.6±0.6	0.722

*SBI-H-GSE: salt-bromine-iodine watery solution with hyaluronic acid and grapefruit seed extract; SD: standard deviation; URTI: upper respiratory tract infections. *: P<0.05.*

Table II. *Comparison of PC-QOL questionnaire average scores and NMTT between the study groups.*

	SBI-H-GSE group N=75		Control group N=65		p-values (between the groups after treatment)
Study Outcomes	**Baseline**	**After treatment**	**Baseline**	**After treatment**	
PC-QOL score, Mean±SD	3.1±0.6	5.4±1.2*	3.4±0.8	4.4±1.1*	0.011*
NMTT (in min), Mean±SD	12.3±1.3	9.6±0.7*	11.9±1.1	10.9±0.9*	0.047*

SBI-H-GSE: *salt-bromine-iodine watery solution with hyaluronic acid and grapefruit seed extract;* ***PC-QOL:*** *Parent Cough-Specific Quality of Life questionnaire;* ***SD:*** *standard deviation;* ***NMTT:*** *nasal mucociliary transport time. *: P<0.05*

Table I. *Demographics and URTIs characteristics of the two study groups.*

	SBI-H-GSE group N=75		Control group N=65		p-values (between the groups after treatment)
Symptoms and signs	**Baseline**	**After treatment**	**Baseline**	**After treatment**	
sensation of having something drip down on to the throat, n(%)	47(62.7)	21(28.0)	42(64.6)	33(50.8)	0.002*
need to frequently clear the throat, n(%)	49(65.3)	24(32.0)	45(69.2)	31(47.7)	0.010*
cobblestone appearance of the nasopharyngeal mucosa, n(%)	33(44.0)	22(29.3)	34(52.3)	27(41.5)	0.094
mucus secretion in the oropharynx, n(%)	62(82.7)	32(42.7)	56(86.2)	38(58.5)	0.027*
nasal discharge, n(%)	58(77.3)	24(32.0)	50(76.9)	32(49.2)	0.033*

SBI-H-GSE: *salt-bromine-iodine watery solution with hyaluronic acid and grapefruit seed extract; SD: standard deviation. *: P<0.05*

Table IV. *Comparison of duration and number of URTI episodes, antibiotic usage and absence from school between the study groups.*

	SBI-H-GSE group N=75		Control group N=65		p-values (between the groups after treatment)
Study outcomes	**Baseline**	**After treatment**	**Baseline**	**After treatment**	
Days with URTI symptoms, Mean±SD	15.6±4.8	10.4±2.7*	15.2±3.5	14.8±3.1	0.023*
Episodes of URTI, Mean±SD	2.7±0.5	2.5±0.6	2.5±0.6	2.5±0.4	0.724
Antibiotic usage (in times), Mean±SD	4.7±0.4	2.5±0.3*	5.2±0.5	4.8±0.4	0.011*
Absence from school (in days), Mean±SD	12.5±3.7	9.4±2.8*	12.9±3.5	10.1±2.7*	0.127

SBI-H-GSE: *salt-bromine-iodine watery solution with hyaluronic acid and grapefruit seed extract;* ***SD:*** *standard deviation;* ***URTI:*** *upper respiratory tract infections. *: P<0.05.*

average score among SBI-H-GSE group than patients treated with normal saline solution and a significant lower prevalence of several symptoms and signs related to PND in the SBI-H-GSE group was noted when compared with controls after treatment period. This is most likely due to a stronger mucus reduction action of the SBI-H-GSE solution compared to normal saline as demonstrated by other studies (15-17) and enhanced by the presence of hyaluronic acid in our watery solution with its positive action on the homeostasis of the upper airways and ciliary motility function (18).

Moreover, when URTIs episodes were taken into account, a significantly lower duration (in days) with URTI symptoms and a lower usage of antibiotic therapy were observed after treatment in SBI-H-GSE group compared to patients treated with the normal saline solution. Apart from anti-catarrhal, anti-inflammatory and normalization action on the upper airways, homeostasis of the salso-bromo-iodine thermal waters, these results were obtained also thanks to the presence of grapefruit seed in our watery solution, with its proven antimicrobial activity (19, 20).

The findings of this study must be interpreted in light of some limitations. PND is primarily a clinical diagnosis that lacks sensitive or specific diagnostic testing and is due to a wide range of conditions, so the risk of bias could be high on enrollment phase, future trials would benefit from more objective and specific tests as further evidence of diagnostic assistance.

Moreover, this study was limited to a single center trial with a short-term follow-up, future work should expand the study population into other larger districts with longer follow-up periods to confirm the result of our study.

CONCLUSIONS

In conclusion, our findings indicate an advantage of salso-bromo-iodine water therapy over normal saline solution in children with URTI disease who refer PND-related symptoms, proving to be an additional nonpharmacological alternative to treat these disorders.

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