

**TITLE: Between GERD and NERD: The Relevance of Weakly Acidic Reflux**

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## **ABSTRACT (Word-count 192)**

Non-erosive reflux disease (NERD) is a common condition and the most frequent phenotype of GERD. NERD is extremely heterogeneous and includes patients with negative endoscopy, but abnormal esophageal acid exposure and/or positive reflux-symptom association analysis (hypersensitive esophagus). This segregation is only possible thanks to the use of impedance-pH monitoring. Indeed, weakly acidic reflux represents one of the most frequent cause of refractory symptoms in patients evaluated off-anti-secretory therapy and, more importantly, during anti-secretory drug treatment. Patients with heartburn who do not have any type of reflux underlying their symptoms (functional heartburn) must be excluded from the category of GERD. The drawbacks of impedance-pH are mainly due to the day-to-day variability of the test and by the fact that the accuracy of the symptom-reflux correlation scores **is** often far from being perfect. Some histopathological characteristics, as dilated intercellular spaces, can be helpful to distinguish patients with NERD by esophageal biopsies. As to the outcome, patients with NERD in whom acid is the main pathogenetic factor respond successfully to PPI therapy, while those with hypersensitive esophagus to weakly acidic reflux could be treated with reflux inhibitors or surgery, although further controlled studies are required.

## Definition of NERD and sub-groups

Heartburn, or retrosternal burning, is a typical symptom of gastroesophageal reflux disease (GERD) that frequently affects a large part of population (10%-20%) in Western countries, interfering significantly with the quality of life of many patients.<sup>1</sup>

For many years, erosive reflux disease has been considered the more common manifestation of GERD, nevertheless, in the past decade it has been realized that erosive reflux disease represents the minority of patients with GERD (~30%), whereas the majority of them (~70%) are included in the non-erosive reflux disease (NERD) phenotype, characterized by the presence of typical reflux symptoms without any esophageal mucosal lesion visible at endoscopy.<sup>2,3</sup>

Pathophysiological studies carried out with 24-hour esophageal multichannel intraluminal impedance–pH testing (MII-pH) have demonstrated that patients with NERD phenotype are markedly heterogeneous and can be subdivided into several well-defined subgroups (after excluding eosinophilic esophagitis, EoE and primary esophageal motor disorders). Currently, the NERD definition includes patients with negative endoscopy but abnormal esophageal acid exposure (AET).<sup>3-7</sup>

Further, in the NERD population, we can include patients with negative endoscopy and normal pathophysiological testing (pH-metry/MII-pH), both for AET and total number of reflux events, but with these latter variables temporarily correlated with symptoms (Hypersensitive esophagus, HE).<sup>7</sup> The correlation between symptoms and reflux events is commonly defined by means of symptom index (SI positive if > 50%) and symptom association probability (SAP, positive if > 95%).<sup>6</sup> Patients may be hypersensitive to both acid and/or non-acid reflux events.<sup>4,8,9</sup> Patients with heartburn refractory to proton pump inhibitors (PPIs), who show negative endoscopy, normal AET and number of refluxes and no correlation between symptoms and reflux, should be considered as patients with functional heartburn (FH)<sup>4,6,7,10</sup> and should not be considered and treated as GERD patients (i.e. stopping any kind of anti-secretory therapy and not undergoing anti-reflux surgery). Accordingly, the last iteration of Rome criteria defined FH as “chronic retrosternal

burning, discomfort or pain refractory to optimal antisecretory therapy in the absence of GERD, histopathologic mucosal abnormalities, major motor disorders, or structural explanations.<sup>7</sup> In line with this definition, Savarino et al.<sup>10</sup> demonstrated the added value of MII-pH in distinguishing patients with GERD from those affected by FH, by showing a 10% diagnostic gain with this technique. Similar results were obtained in some studies performed both “off PPI therapy”<sup>8, 11-14</sup> (10-15% diagnostic gain) and “on PPI therapy”<sup>11, 12, 15, 16</sup> (20-40% diagnostic gain) with MII-pH testing. Overall, the added values and the clinical application of impedance monitoring should help the clinicians to correlate an increased number of symptoms with reflux events, thus increasing the number of patients with reflux disease and reducing the rate of patients with FH.

### **Clinical characteristics**

The positive or negative response of patients with heartburn to PPI therapy is an empiric criterion, which can include or exclude from the definition of GERD those patients who complain of heartburn and do not have an objective demonstration of the presence or absence of gastro-esophageal reflux. However, it has been estimated that 25%-40% of patients complaining of heartburn continue to present symptoms despite daily PPI use and that there is a large group of patients with functional disorders rather than GERD who may respond to PPI due to a placebo effect.<sup>5, 17</sup> Previous studies have underlined this important limitation, which affects the diagnostic accuracy of the PPI test.<sup>18, 19</sup> In particular, Bytzer *et al.*<sup>20</sup> carried out a study in a sample of well-defined primary care patients with suspected GERD, and demonstrated the limited ability of a PPI trial to identify patients with GERD, using endoscopy, esophageal pH-metry and reflux disease questionnaires as reference standard. Presence or absence of gastro-esophageal reflux during barium esophagography does not correlate with incidence or extent of reflux observed during MII-pH monitoring and it is not of value for the diagnosis of GERD.<sup>19, 21</sup>

A symptom-based approach using a questionnaire (GERDQ) does not always confirm GERD diagnosis.<sup>22, 23</sup> Multiple studies have demonstrated that patients with objective evidence of

reflux tend to be older, male, and smokers in comparison to patients with FH.<sup>24-27</sup> Increased body mass index ( $>25 \text{ kg/m}^2$ ) is also associated with PPI failure in patients with acid reflux compared with those patients with HE or FH.<sup>27-29</sup> Further, there are **several** evidences suggesting a strong association between FH and other functional disorders such as functional dyspepsia and/or irritable bowel syndrome, emphasizing the hypothesis of a unique “whole gut” GI disorder.<sup>30-32</sup>

However, currently, demographics do not reliably distinguish subgroups of patients suffering from heartburn.<sup>25, 33</sup> Understanding the epidemiology and pathogenesis of patients with FH may allow early recognition of these patients and could help to anticipate and avert therapeutic failure.<sup>34</sup>

### **MII-pH diagnosis and different GERD phenotypes**

Patients often undergo extensive functional testing to evaluate heartburn if there is inadequate response to optimal acid suppressive therapy, as this approach seems to be useful in differentiating FH from refractory acid reflux. To note, optimal acid therapy is not well-defined in the literature. In the setting of objective acid testing, an effective therapy may be considered the adequate control of acid assessed by a functional examination. However, a simple and more often used definition for optimal acid suppression is the lack of symptoms in response to acid suppression (defined as twice a day proton pump inhibition).<sup>6, 35</sup>

The complete chemical nature of reflux can be detected neither by traditional esophageal pH-metry nor by the catheter-free Bravo™ system,<sup>36</sup> but the advent of 24 h MII-pH testing has enabled differentiation of acid (**reflux with pH<4**) from weakly acidic ( $4 < \text{pH} < 7$ ) or **weakly alkaline reflux (pH>7)**.<sup>37</sup> Indeed, reflux of gastric content into the esophagus is a physical event that has been evaluated for long time only by means of techniques able to obtain information on the chemical component of refluxate. The MII-pH was an innovative technique that provided a detailed characterization of each reflux event including chemical (**acid, weakly acidic/alkaline reflux**) and physical properties (liquid, mixed, gas).<sup>37, 38</sup> In the last decade, it has been shown that nonacid

reflux (**weakly acidic and weakly alkaline reflux events**) represents the majority of reflux episodes in patients with GERD on PPI therapy.<sup>39, 40</sup> Indeed, the total number of reflux episodes is not affected by acid suppressive therapy, and weakly acidic reflux accounts for approximately 90% of all reflux episodes in patients on PPIs, thus representing a potential mechanism underlying the failure of PPI treatment in patients with reflux-related symptoms.<sup>12, 15</sup> Further, the assessment of both acid and non-acid reflux correlation with symptoms may allow us to better select patients who would benefit from anti-reflux surgery or an endoscopic anti-reflux procedure.<sup>41</sup>

However, all of the available tests for GERD diagnosis have some limitations. The drawbacks of MII-pH are mainly due to the day-to-day variability of the test.<sup>42-44</sup> Additionally, the reflux-symptom correlation in patients with GERD who do not respond to PPI therapy is actually calculated by the symptom index (SI) or symptom association probability (SAP), although their validity is still uncertain.<sup>45, 46</sup> Unfortunately, symptoms may not occur during 24-hour reflux monitoring. Moreover, the **accuracy** of patients in symptom recording is often far from perfect. As a consequence, SAP/SI may be negative even in several patients with erosive reflux disease (ERD).<sup>16, 47-49</sup> Therefore, in pH-negative patients a positive SAP/SI indicates reflux-related heartburn,<sup>4, 50</sup> but a negative SAP/SI does not exclude GERD; indeed, patients with heartburn may respond to PPI therapy despite normal MII-pH findings.<sup>51</sup> Accordingly, Zerbib et al.<sup>52</sup> reported that MII-pH results were not always able to predict the response to PPIs in patients with typical reflux-related symptoms, when the test was performed off PPI therapy.

Recently, the ability of MII-pH testing in better understanding GERD pathophysiology has improved by means of new parameters, such as the post-reflux swallow-induced peristaltic wave (PSPW) index, which indicates the efficacy of esophageal clearance,<sup>47</sup> and the baseline impedance values, which indicate lack of integrity in the esophageal mucosa.<sup>16, 39, 47, 53, 54</sup> PSPW index has been shown to be lower in patients with abnormal AET, compared to healthy volunteers (HVs) or FH.<sup>47</sup> Moreover, this parameter was not altered after medical or surgical therapy.<sup>55</sup> Further, Kessing et al.<sup>55</sup> described lower values of baseline impedance levels in the distal esophagus of patients with

abnormal esophageal AET, compared to HVs. Recently, many studies standardized the measurement of baseline impedance by calculating the mean nocturnal baseline impedance (MNBI) across three 10-min periods between 1 AM and 3 AM, away from daytime esophageal physiologic activity.<sup>48, 51, 56</sup> The most relevant advantages regarding both the MBNI and PSPW index have been recently published by Frazzoni et al.<sup>48</sup> The authors showed a gradient behaviour of them across 289 GERD patients and 50 healthy controls, being both parameters worse in erosive esophagitis compared with NERD and healthy controls. The diagnostic yield of both parameters was greater than that of increased AET, total reflux events, and bolus exposure time in both erosive esophagitis and NERD. Furthermore, MNBI and PSPW index make pathophysiologic sense, and certainly deserve a chance in redeeming the clinical value of ambulatory MII-pH testing.<sup>57</sup>

There are still others information that could be caught from a more in deep analysis of MII-pH tracing such as the role of bolus contact time in improving GERD diagnosis<sup>58</sup> or gas and mixed reflux or supragastric belching in increasing symptom perception.<sup>59, 60</sup> Further, the role of this technique in the management of patients with extraesophageal GERD has been partially investigated.<sup>61-67</sup>

### **Weakly acidic reflux and refractory heartburn**

The Porto consensus report provided a detailed nomenclature for reflux patterns detected by MII- pH monitoring.<sup>37</sup> An impedance-detected reflux is defined as acid when the esophageal pH falls to  $< 4$ , or when reflux occurs with the esophageal pH already  $< 4$ . When the esophageal pH falls by  $\geq 1$  unit, but remains  $> 4$ , it is considered “weakly acidic reflux.”

The prevalence of weakly acidic reflux (**WARs**) in refractory GERD depends on the way reflux monitoring is performed. Although several **WARs** episodes can be detected during 24-hour MII-pH monitoring “off” PPI, this type of refluxate becomes particularly significant during studies “on” PPI.<sup>12, 15, 68, 69</sup> **First of all**, Vela et al.<sup>69</sup> used stationary MII-pH monitoring to compare **3-h** postprandial recordings of the same subject “on” and “off” PPI. The antisecretory treatment



provoked no reduction in the total number of reflux events, but there was a shift in the refluxate's pH from acidic to weakly acidic. Heartburn was replaced by regurgitation, which became the predominant symptom in these patients. **Similarly and by means of the more reliable 24-hour pH-impedance monitoring, Frazzoni and co-workers showed that WARs are the predominant reflux events in patients evaluated on-PPI.**<sup>16, 39, 54</sup>

Studies in patients with refractory GERD showed that WARs could be associated with 30%-40% of symptoms.<sup>12, 15 16, 54</sup> In another study Zerbib et al,<sup>70</sup> observed that in a group of patients with refractory heartburn WARs were associated to both heartburn and regurgitation in patients evaluated on double dose PPI therapy. The role of WARs in patients with typical refractory symptoms has been studied, almost always, in patients on PPIs. Few but intriguing data have been reported on WARs evaluated in patients off-therapy and it was confirmed that this type of chemical reflux can be associated with both heartburn and regurgitation.<sup>49, 71, 72</sup>

**A prospective study in well selected PPI responder and non-responder NERD patients, in whom MII-pH was performed both off an on-PPIs,<sup>73</sup> showed that WAR accounted for approximately 30% of symptomatic refluxes both in non-responder and in responder patients whereas an overall increased number of reflux episodes and an enhanced sensitivity to all episodes could predict treatment failure. Comparable findings were reported in consecutive refractory patients - 50% of them affected by erosive esophagitis - undergone laparoscopic fundoplication<sup>16</sup> and repeated MII-pH monitoring performed on PPIs before treatment and off PPIs at follow up. In that series, the 3-year outcome assessment revealed that decrease of the abnormal number of all reflux episodes (also due to a decrease of WARs), normalization of acid exposure and of SAP/SI were associated with a sustained symptom remission.**

The mechanisms by which WARs can provoke persistence of symptoms remain controversial, as several factors have been proposed: (1) esophageal distension by increased reflux volume,<sup>70</sup> (2) persistent impairment of esophageal mucosa due to weakly acidic reflux containing bile acids,<sup>74</sup> (3) **the proteolytic activity of pepsins that is maintained up to pH 6<sup>75</sup> and healing of**

mucosal breaks occurs through reparative processes that are inhibited at pH 6.5 and abolished at pH 3.0,<sup>75</sup> (4) esophageal hypersensitivity to non-acid components of gastric contents either when gas is present in the refluxate or after esophageal sensitization due to an acid reflux<sup>76, 77</sup> and (5) reduced esophageal chemical clearance.<sup>78</sup> Once refluxate has entered the esophagus the main defense against persistence of mucosal damage is removal of the noxious agents as quickly as possible: indeed, defective chemical clearance of WARs, which represents the vast majority of reflux events in PPI-refractory GERD, has a key role in the pathogenesis of PPI-refractory reflux esophagitis.<sup>47, 78</sup>

By the way, there is no doubt that WARs can be one of the underlying mechanisms of refractory GERD. Indeed, a cause-and-effect relationship between WARs and PPI-refractory heartburn/regurgitation has been shown in some prospective observational studies addressing post surgical outcome in PPI-refractory typical GERD.<sup>16, 54</sup> These studies well evidenced that WARs might be considered the major determinant of typical GERD-related symptoms in PPI-refractory patients. Anyway, future prospective studies should be addressed to confirm these data in a larger series of patients.

### **Histopathology changes and mucosal barrier integrity in NERD subgroups**

The integrity of the mucosal epithelial barrier is of great importance to prevent pathologic consequences of reflux, and can be overcome in the disease state (whether erosive or non-erosive). So, it is of relevance to discuss the structures responsible for maintenance of mucosal integrity.

The pre-epithelial defense consists of a small water layer with limited buffering capacity, presumably due to the presence of bicarbonate derived from swallowed salivary fluid and from secretions of esophageal submucosal glands.<sup>79</sup> In patients with esophagitis there is a clear breach in this barrier allowing components of the refluxate to reach the nociceptors in the lamina propria.<sup>79</sup> Acid and acid-pepsin initially attack and damage the intercellular junctions, thus resulting in an increase in para-cellular permeability, reflected morphologically by the presence of dilated intercellular spaces.<sup>80</sup>

From a diagnostic point of view, esophageal biopsies might be helpful to identify patients with histological signs of GERD. Further, it is relevant to underline that the addition of esophageal biopsies as an adjunct to an endoscopic examination has been re-emphasized because of the progressively increased **detection** of eosinophilic esophagitis (EoE). Many clinicians routinely take esophageal biopsies in patients with reflux-type symptoms to search for EoE in the setting of an endoscopy that does not reveal erosive changes.<sup>81</sup>

Histological examination of esophageal biopsies may help in distinguishing patients with NERD from FH, as dilated intercellular spaces can be a microscopic marker of reflux and esophageal damage frequently associated with NERD and only rarely with FH.<sup>82</sup> The presence of dilated intercellular spaces may also predict a non-response to acid suppression.<sup>83</sup> Using light microscopy (LM), it is possible to combine multiple histological alterations denoting the presence of microscopic esophagitis (ME), such as basal cell hyperplasia, papillae elongation, and DIS.<sup>84-86</sup>

Zentilin et al.<sup>85</sup> proposed a histological score able to discriminate between GERD and controls with a positive predictive value of 97% and a negative predictive value of 46%.

It has been also hypothesized that there is a good correlation between DIS in the esophageal epithelium of both ERD and NERD patients and the presence of heartburn.<sup>87</sup> Recently, Savarino et al.<sup>88</sup> demonstrated the lack of microscopic esophagitis (ME) in the esophageal distal biopsies of FH patients, suggesting a limited role of these histological abnormalities in symptom generation in them. ME can be considered as an accurate and reliable diagnostic marker for distinguishing FH patients from GERD patients and has the potential to be used to guide the correct therapy.

Fiocca et al.<sup>89</sup> developed consensus guidelines for histologic recognition of ME in patients with GERD and proposed several criteria, which achieved high levels of agreement when assessed independently by 5 pathologists.

Recently, Kandulski et al.<sup>90</sup> confirmed that esophageal biopsies are useful to differentiate NERD from FH, especially in patient with refractory heartburn. The same authors showed that low levels of baseline impedance (detected with 24-h MII-pH) are associated with increased exposure to

acid and dilation of intercellular spaces, indicating a strong correlation between esophageal mucosal impairment and baseline impedance.<sup>91</sup>

However, these histological alterations are not still adequately sensitive and specific to be used in a diagnostic algorithm, and so far routine esophageal biopsies as a means of making a sound diagnosis of FH are not recommended.

### **Aerophagia, gas reflux and supragastric belching in pathophysiology of NERD**

Aerophagia is a condition of excessive air swallowing, which goes to the stomach. Poudroux et al.<sup>92</sup> observed, by means of ultrafast computerized tomography, a substantial aerophagia (8-32mL of air) during transit of a swallowed bolus through the esophagus and a partial bolus separation with air preceding fluid. Bravi et al.<sup>93</sup> demonstrated that PPI non-responder patients with GERD swallowed more air at mealtime than those who respond to PPI treatment and also have more reflux episodes that contain gas. The authors concluded that air swallow combined with mucosal sensitization could affect perception of symptoms.

Gastric belching (frequent gas-reflux events during MII-pH 24-h) is the escape of swallowed intragastric air that enters the esophagus during a transient lower-esophageal sphincter relaxation (TLESR).<sup>94</sup> Gastric belches occur 25 to 30 times per day and are physiological, involuntary and controlled entirely by reflexes. Belching does not seem to facilitate acid reflux in healthy subject.<sup>95</sup> On the other hand, the presence of gas into the refluxate enhances reflux perception, is frequently associated with proximal extent of reflux and occurs more frequently in patients who do not respond to acid suppressive treatment.<sup>71, 77, 93, 96</sup>

In supragastric belches the air does not originate from the stomach but is ingested immediately before it is expelled again.<sup>97</sup>

Supragastric belches are not a reflex but, instead, are the result of human behavior. Studies with simultaneous impedance monitoring and high-resolution manometry reveal the underlying mechanism of this behavior: a contraction of the diaphragm creates a negative pressure in the

thoracic cavity and the esophagus, subsequent relaxation of the UES, resulting in inflow of air into the esophagus.<sup>98</sup> It is unclear what causes supragastric belching and what causes patients to start this behavior. Some patients report that initially they belched purposefully to relieve a sensation of bloating or abdominal discomfort but that with time they lost control of the belching. Many patients stop belching during speaking and sleeping; it has been shown that distraction also reduces the frequency of belching,<sup>97</sup> whereas putting attention to their belching behavior usually results in an increase in belching frequency.<sup>97</sup> Recently, Koukias et al.<sup>60</sup> described 100/2950 patients, over a 4 years period, with supragastric belching that were associated more frequently with pathological acid exposure and esophageal hypomotility.

Speech therapy has been proposed in a recent pilot study including 11 patients and resulted to be beneficial.<sup>99</sup> Similar positive results have been reported with behavioral therapy in another study.<sup>100</sup> Baclofen has also been applied with success in a small open label study.<sup>101</sup>

### **Medical and surgical treatment in NERD, hypersensitive esophagus and functional heartburn**

Patients presenting with symptoms suggestive of reflux disease are often empirically treated with lifestyle advices and acid suppressive drugs, including PPIs.<sup>102-105</sup> When patients do not respond to standard therapy, endoscopic and functional testing is performed to challenge the initial diagnosis and to investigate the reasons of treatment refractoriness. While the presence of erosive esophagitis confirms the diagnosis, a negative endoscopy cannot be used to rule out reflux disease, as a substantial part of GERD patients do not have any abnormalities seen on endoscopy (NERD).<sup>106, 107</sup>

In most clinical trials, NERD patients are defined only by the presence of typical reflux symptoms and negative endoscopy. However, without appropriate functional testing it is difficult, if not impossible, to distinguish between FH, functional dyspepsia, and true NERD. Thus, the heterogeneity of the trial participants across studies could cause underestimation of the response rates to PPI treatment in NERD. Indeed, in a recent meta-analysis, Weijenborg et al. observed that

in well-defined NERD patients (diagnosed by means of endoscopy and pathophysiological tests), the estimated complete symptom response rate after PPI therapy is comparable to the response rate in patients with ERD. In this paper the authors concluded that the previously reported low response rate in studies with patients classified as NERD was likely the result of inclusion of patients with upper gastrointestinal symptoms that did not have reflux disease.<sup>108</sup>

Previously, Fass et al.<sup>109</sup> observed a direct and strong correlation between acid exposure time and the positive response rate to omeprazole (40 mg in the morning and 20mg in the evening).

Zerbib et al.<sup>52</sup> described that patients with either positive symptom–reflux association analysis or AET>5% were more frequently associated with a positive response to PPI therapy. However, the main finding of this study was that performing the multivariate analysis, the only factors associated with inadequate response to PPI were BMI  $\leq 25$  kg/m<sup>2</sup> and the presence of functional dyspepsia or irritable bowel syndrome symptoms. Patel et al.<sup>110</sup> observed that only acid-based reflux parameters (total AET and AET>4.0%) offer greater value over impedance-based nonacid-reflux parameters (total reflux events and bolus exposure time) in predicting symptomatic responses to PPI therapy.

Controlling heartburn in patients with NERD can also be achieved with antacid or alginate compounds. Many clinical trials have demonstrated the benefit of these drugs, which continue to have a role in quickly relieving typical reflux symptoms in both NERD and erosive reflux disease.<sup>111-117</sup> However, these over-the-counter drugs need multiple doses during the day, because of their short duration of action. Sodium alginate is a polysaccharide derived from seaweed. It binds water to form a viscous gum that floats in the proximal stomach, thereby **separating the acid pocket from the distal esophagus.**<sup>118</sup> **Some commercially** available alginate preparations also contain an antacid. Sodium alginate might have the theoretical advantage of blocking both acid and WARs on the basis of the mechanical formation of a raft floating above gastric secretions, but its effect on the latter kind of reflux was not confirmed in a study using MII–pH testing.<sup>119</sup> As above-mentioned, most reflux episodes happen during TLESRs, and these can be inhibited pharmacologically. The  $\gamma$ -

aminobutyric acid (GABA)<sub>B</sub>-receptor agonist baclofen reduces the incidence of TLESRs and reflux episodes. Vela et al.<sup>120</sup> have shown that baclofen induces a reduction of total amount of reflux events and contributes to improve the symptoms complained of by patients with reflux. On the other hand, this drug is not suitable for treatment of GERD because of its mainly neurologic central side-effects.<sup>121</sup> Unfortunately, the development of new drugs of this type with less severe adverse events than baclofen has been stopped, because of poor efficacy.<sup>122</sup>

An additional therapeutic option might be surgery that should be considered for patients with proven GERD and for those patients with weakly acidic reflux events.<sup>16, 123, 124</sup>

Five-year results of a randomised European trial comparing maintenance PPI treatment (esomeprazole) with laparoscopic Nissen fundoplication<sup>125</sup> showed that the remission rate did not differ between the two therapeutic strategies. However, at 5 years, acid regurgitation was more prevalent in the PPI group than in the fundoplication group.

Several uncontrolled trials have shown that fundoplication is able to control symptoms related to both acid and WARs<sup>16, 41, 54, 126, 127</sup> In particular, Broeders et al.<sup>126</sup> have demonstrated that patients with normal AET and positive symptom association (HE patients) might benefit from fundoplication as well as patients with abnormal AET, **although an important limitation of this study should be reported in that about 40% of the HE patients had prior evidence of erosive esophagitis at endoscopy (i.e. not affected by HE per definition). Similarly, Patel et al.<sup>128</sup> showed that anti-reflux medical and surgical therapy may improve symptoms in hypersensitive patients, in well-defined settings.** Bredenoord et al.<sup>129</sup> confirmed that fundoplication is able to reduce the abnormal levels of both chemical types of reflux. Patel et al.<sup>130</sup> demonstrated in a large series of patients, after a 40-month follow-up period, that the response to laparoscopic anti-reflux therapy was consistent in patients selected by means of a MII-pH performed off-therapy. The authors showed that abnormal AET and the symptom-reflux association SAP consistently predicted symptomatic outcome in a multivariate analysis.

Few data are available regarding characteristics of the refluxate, such as the presence of pepsin and bile acids that may contribute to symptom perception.<sup>131</sup> In this review we focused that WARs events can cause not only regurgitation but also heartburn<sup>5, 71</sup> and patients with symptomatic non-acid (weakly acidic) reflux on PPI treatment should be considered good candidates for anti-reflux surgery.

## Conclusions

Gastroesophageal reflux disease is a very common condition. Heartburn and regurgitation are the symptoms of the typical reflux syndrome. Reflux characteristics, other than acidity, such as the presence of WARs and presence of pepsin may also contribute to symptom perception. The cornerstone for treatment of GERD-related symptoms is acid suppression with PPIs. In tertiary care center it is more frequent running into patients unresponsive to acid suppressive treatment. The lack of response to a sustained acid inhibition suggests that the symptoms are not due to reflux or, alternatively, that they are reflux-related but PPI-unresponsive. Pathophysiological diagnosis of GERD should be performed preferably by means of combined pH-impedance measurement. Patients should be recommended to accurately record symptoms to obtain the best information from symptom-reflux correlation scores. Up and coming parameters obtained from impedance and pH tracings as well as the presence of gas, aerophagia and supragastric belching should be considered, particularly when patients fail to record symptoms before considering functional diagnosis. Future studies are needed on these topics.

When NERD patients have been well characterized, PPI treatment as well as antireflux surgery can be considered effective in them. It has been shown that a proportion of patients with reflux hypersensitivity can improve with antireflux surgery, especially if regurgitation is the main symptom and some structural disruption at the esophago-gastric junction may be documented.<sup>132-134</sup>. At present functional upper GI symptoms are an exclusion criterion for antireflux surgery.



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**Conflicts of interest**

The authors declare no conflicts of interest.

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