Gastro Esophageal Reflux Disease: An Imperfect Diagnosis

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Abstract

Gastroesophageal Reflux Disease (GERD) is a common problem, with a prevalence ranging between 10% and 20% according to the geographic area, which is expensive to diagnose and treat in both primary and tertiary care settings. Diagnosing GERD poses many problems: firstly, gastroesophageal reflux may be a physiologic phenomenon, and hence a quantitative and not qualitative test is needed. Secondly, symptoms are rather unspecific and it may be difficult to link them to GERD, particularly in the setting of extraesophageal manifestations. Endoscopy is very useful when complications are found, namely erosions, ulcers or Barrett's metaplastic epithelium, yet the majority of patients with GERD have a Negative Endoscopy (so called NERD) despite typical symptoms. Esophageal 24h pH-monitoring and pH-impedance examinations have greatly increased the diagnostic yield, but they are not universally available and are quite expensive. Finally a PPI test may be attractive in the setting of general practitioner, but its sensitivity and specificity are rather poor. In conclusion, we still face a disease which has only imperfect ways of truly being diagnosed.

Introduction

Gastroesophageal Reflux Disease (GERD) is a common problem which is expensive to diagnose and treat in both primary and tertiary care settings. The annual direct and indirect cost for managing this disease is estimated to be more than US $14 billion in the USA, of which 60% is spent on drugs [1].

Unfortunately, there is no gold standard test for GERD. Since the reflux of acid, particularly after meals, is a physiological process, the simple presence of Gastroesophageal Reflux (GER) or occasional symptoms of heartburn or acid regurgitation cannot be defined as a disease.

Recently, a group of 44 experts from 18 countries used a modified Delphi process to develop a globally acceptable definition and classification of GERD which can be applied in both clinical practice and research (Figure 1) [2]. This international group defined GERD as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications". Troublesome symptoms are defined by the patient to affect their quality of life. Mild symptoms occurring two or more days a week, or moderate to severe symptoms occurring more than one day a week, are often considered troublesome by patients. The group further divided the manifestations of GERD into esophageal and extraesophageal syndromes, with extraesophageal syndromes divided into established and proposed associations.

According to this new global GERD definition, patients may be diagnosed based on typical symptoms alone or on tests demonstrating abnormal reflux of stomach contents (e.g., pH testing, impedance-pH monitoring) or the injurious effects of the refluxate on esophageal mucosa (e.g., endoscopy, histology) in the presence of typical or atypical symptoms or complications.

In primary care, most patients are initially uninvestigated and will present with 'symptomatic syndromes' either typical reflux complaints of heartburn and/or regurgitation or reflux-related chest pain. After investigation, usually endoscopy with histology, patients can be further classified as having the 'syndromes with mucosal injury', including reflux esophagitis, stricture, Barrett's esophagus and/or esophageal adenocarcinoma. Thus, the proposed consensus definition allows symptoms to define the disease but permits further characterization if mucosal injury is found. This group also recognized laryngitis, cough, asthma and dental erosions as possible extra-esophageal syndromes of GERD. However, the statement was restrained in defining a causal relationship due to the lack of high level evidence, especially showing a beneficial effect of reflux treatments on the

Table 1: Diagnostic tests for Gastroesophageal Reflux Disease, existing tests can be divided into tests for reflux, tests to assess GERD symptoms and tests to assess esophageal mucosal damage.

Tests for reflux
Intraesophageal pH monitoring
Ambulatory bilirubin monitoring (bile reflux)
Ambulatory impedance and pH monitoring (non-acid reflux)
Barium esophagram
Oropharyngeal pH monitoring-Restech
Tests to assess symptoms
Empirical trial of PPIs
Intraesophageal pH monitoring with symptom analysis
Ambulatory impedance and pH monitoring with symptom analysis
Tests to assess esophageal mucosal damage
Endoscopy
Esophageal mucosal biopsy
Barium esophagram

Table 2: Causes of PPI-refractoriness in GERD [46].

Erroneous diagnosis of GERD
Functional dyspepsia
Functional heartburn
Functional chest pain
Rumination syndrome
Aerophagia
Vomiting
Achalasia
Esophageal obstruction
Non-acid reflux
Esophageal hypersensitivity
Therapy non-compliance
Limited effectiveness of proton pump inhibition
Nocturnal acid breakthrough
Rapid metabolism
Zollinger-Ellison syndrome
Post-surgical problems

extra-esophageal syndromes and the reality that these syndromes are usually multifactorial with GERD as one of several potential aggravating co-factors.

Diagnosis of GERD

A large number of tests are available for evaluating patients with suspected GERD (Table 1) [3].

However, the lack of a gold standard has hampered the assessment of the accuracy of various approaches to the diagnosis of GERD [4] and, hence, GERD has recently been defined as an "imperfect diagnosis" [5]. The most striking feature of these tests, as considered globally, is the fact that they are at the same time redundant and imprecise, since they are often necessary but they are affected by limited diagnostic accuracy (i.e. low sensitivity, although high specificity).

As stated by the Montreal Classification, the presence of frequent heartburn and acid regurgitation is sufficiently accurate to identify the disease and begin medical treatment. In the ordinary practice, this is not always the case, and clinicians must decide which tests to choose so as to make the diagnosis in a reliable, timely, and cost-effective manner, depending on the information desired [3]. Recent guidelines published by the American Gastroenterological Associations invoke diagnostic testing in 3 broad scenarios: (1) to avoid misdiagnosis, (2) to identify complications of reflux disease, and (3) in the evaluation of empirical treatment failures [6].

In this review, we will consider the role and priority of most commonly used diagnostic tests for GERD (i.e., endoscopy, symptom assessment, ambulatory pH-(impedance) monitoring, and the Proton-Pump Inhibitor (PPI) test) in the evaluation of patients with suspected esophageal GERD syndromes, with a particularly mention on the more recent tests that became available for our clinical practice (i.e., Peptest and the ambulatory oropharyngeal reflux monitoring). We will not touch herein the issue of the evaluation of patients with suspected extra-esophageal GERD syndromes.
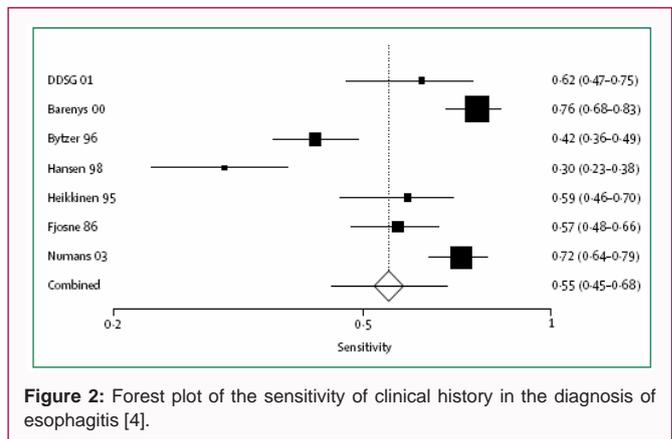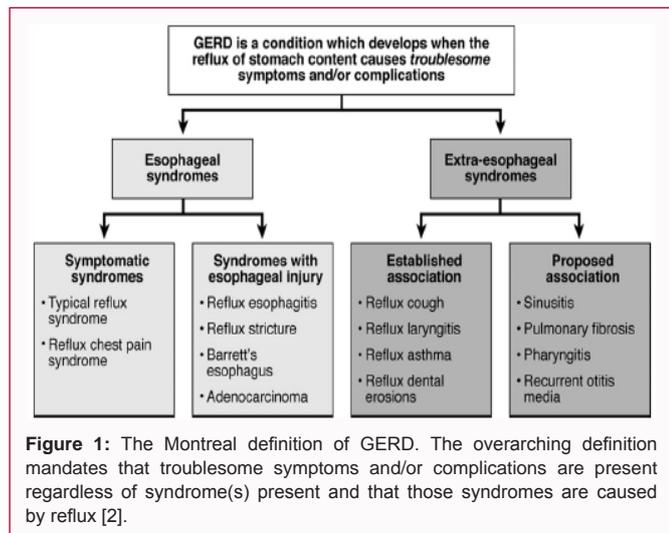
Endoscopy

The identification of esophagitis with upper gastrointestinal endoscopy is highly specific (90% to 95%) [4] for GERD, but has a sensitivity of only around 50% [7]. The extent of mucosal injury can be assessed at endoscopy and this has been categorized into grades A to D according to the Los Angeles classification [8]. About 30% to 50% of patients with the disease will have a normal endoscopy in referral centers, but in primary care and the general population the rate of esophagitis is lower [9]. Endoscopy can also evaluate

any complications of the disease, such as stricture or Barrett's esophagus, and is recommended if patients have alarm features with reflux symptoms. Alarm features dictate circumstances in which diagnostic testing is indicated as part of the initial evaluation, either because they suggest that complications of GERD are present or because they suggest an alternative diagnosis. Important alternative diagnoses include coronary artery disease, gallbladder disease, gastric or esophageal malignancy, peptic ulcer disease, and eosinophilic, infectious, or caustic esophagitis. Proposed alarm features include vomiting, evidence of gastrointestinal blood loss, involuntary weight loss, dysphagia, anemia, chest pain, or epigastric mass [10]. High-quality evidence supporting the broad utility of alarm features as a diagnostic tool is quite limited (US Preventive Services Task Force [USPSTF-see Appendix] grade Insufficient). A recent meta-analysis addressed the specific issue of the utility of alarm signs and symptoms in diagnosing upper gastrointestinal malignancy based on 15 published prospective evaluations encompassing 46,161 patients [10], 8,669 with one or more alarm feature, and 150 subsequently found to have gastric or esophageal cancer on endoscopy. The authors reported an overall pooled sensitivity and specificity of 67% (95% confidence interval, 54% to 83%) and 66% (95% confidence interval, 55% to 79%), respectively [10]. Individual alarm features with the best performance were weight loss, dysphagia, and epigastric mass on examination. The AGA guidelines above recalled claim that, if judged significant, any of the alarm features, if present, should be evaluated with endoscopy (USPSTF grade B, quality fair). Dysphagia merits special consideration as an alarm symptom because it can be indicative of a stricture or malignancy. However, dysphagia was also reported by 37% of 11,945 patients with esophagitis without stricture or Barrett's esophagus participating in esophagitis clinical trials, and it resolved in 83% of cases with PPI therapy [11]. This discrepancy led the Montreal consensus group to suggest that not all dysphagia, but only "troublesome" dysphagia, warrants investigation [2] (US Preventive Services Task Force [USPSTF] grade B, quality fair). Troublesome dysphagia is present when patients need to alter their eating patterns, when patients have symptoms of solid food getting impacted, when it exhibits a worsening pattern, or when it does not resolve with PPI therapy. A final caveat in the endoscopic evaluation of dysphagia is that the endoscopist should obtain multiple (preferably 5) esophageal mucosal biopsy specimens or even biopsy specimens from multiple levels to investigate for eosinophilic esophagitis [12]. The increasing recognition of eosinophilic

Figure 1: The Montreal definition of GERD. The overarching definition mandates that troublesome symptoms and/or complications are present regardless of syndrome(s) present and that those syndromes are caused by reflux [2].

Figure 2: Forest plot of the sensitivity of clinical history in the diagnosis of esophagitis [4].
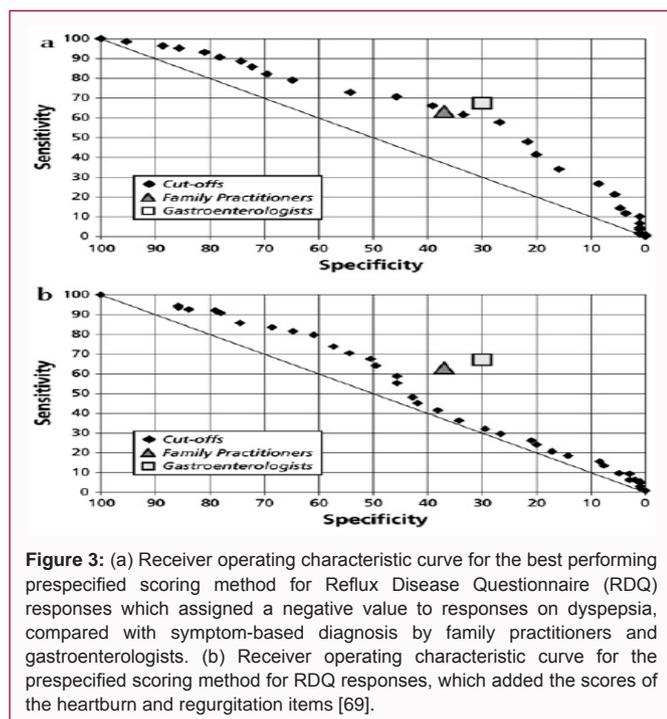
esophagitis as a confounding clinical entity has increased somehow the value of biopsies when performing upper endoscopy for GERD [13,14]. Given the high rate of eosinophilic disease in the setting of dysphagia without an obvious obstructing lesion, such subjects may benefit from mucosal biopsies (USPSTF grade B, quality fair) [15]. No evidence demonstrates the utility of routine esophageal biopsies in the setting of reflux symptoms without dysphagia [6]. Finally, as to the utility of distal esophageal biopsies just to diagnose GERD, recent studies revealed that dilated intercellular spaces on optic or electron microscopy in the majority of Non-Erosive Reflux Disease (NERD) patients that could facilitate activation of nociceptive visceral afferent nerve receptors and that may be used as diagnostic marker of GERD, at least for distinguishing refractory patients with GERD from those with functional heartburn [16-18]. However, although such changes could be sensitive diagnostic markers of GERD, they required specialist equipment and histology while the utility of these findings in clinical practice has not been determined. Finally, recent studies have shown that high-resolution endoscopy with narrow band imaging reveals micro-erosions and other subtle abnormalities at the esophageal gastric junction in Non-Erosive Reflux Disease (NERD), but the value of this finding has to be further validated and elucidated [19].

pH-monitoring and pH-impedance monitoring

Ambulatory pH monitoring has been in use for many years to detect and/or confirm abnormal levels of acid reflux in the esophagus and to correlate patients' symptoms with Esophageal Acid Exposure (EAE). Previous clinical guidelines have concluded that ambulatory pH monitoring is useful "to confirm GER in patients with persistent symptoms without evidence of mucosal damage, especially when a trial of acid suppression has failed" [20]. The clinical problem here is to ascertain whether therapy has failed because of troublesome symptoms attributable to reflux that did not resolve with current PPI therapy or because the symptoms under consideration are not attributable to reflux. In current practice, this dilemma is usually faced when the patient has already been treated with twice-daily PPI therapy for a significant period and it is unlikely that endoscopy will reveal esophagitis or the examination has been negative.

Sometimes called the 'gold standard' of GERD diagnosis, studies have shown that conventional ambulatory pH monitoring has several major shortcomings that limit both its sensitivity and specificity.

Concerns about sensitivity are highlighted by the observation that as many as 23% of patients with endoscopically detected esophagitis may demonstrate distal EAE values that fall within the normal range [21]. While many other studies have reported higher sensitivities of pH monitoring that approximate 90% for Erosive Esophagitis (EE) patients, the sensitivity of pH monitoring in patients with NERD is significantly lower, raising questions as to how to best define GERD in the absence of erosions [22]. The sensitivity problems of pH monitoring are multifactorial in origin and include reduced patient physical and dietary activity during the recording period owing to nasal and pharyngeal irritation of the pH catheter, day-to-day variability in acid exposure, and problems of appropriate pH electrode positioning in the esophagus. Some of these problems may be reduced by using a wireless pH-monitoring system, the so-called Bravo capsule monitoring system [23], which provides several advantages over conventional pH monitoring. Because the capsule is affixed to the transnasal mucosa, it avoids proximal or distal catheter displacement encountered with the conventional system. The absence of the transnasal catheter also improves patient tolerability and compliance with normal physical and dietary activities [24,25]. Finally, the Bravo system allows for prolonged monitoring of esophageal pH over a 48-h period. This may help improve the diagnostic accuracy of pH monitoring for GERD because it increases the likelihood of patients experiencing both symptoms and reflux events during the test period [24,26]; in particular, the Bravo system has been shown to increase the diagnostic sensitivity for both reflux events and symptom association [24,27] and allows for extended monitoring in patients both on-and off-therapy in a single study. However, this latter technique has also some important drawbacks compared to the catheter-based system, including the reduced ability to detect short reflux episodes (i.e., decreased ability to diagnose abnormal EAE) [28], the variable placement in the distal esophagus with consequent risk of early detachment (5%) [29], the temporary occurrence of chest-pain symptom after positioning the capsule, the risk of retention in the gut and the higher costs [30]. Anyway, the major limitation of both conventional pH monitoring and Bravo system is the lack of detection of non-acid (or weakly acid) reflux; this has prompted to the use of pH-impedance esophageal recording, a new paradigm of continuous physical and chemical monitoring of gastric refluxate into the esophagus [31]. Using electrodes mounted on a standard esophageal pH monitoring catheter, impedance monitoring allows clinicians to detect the composition, distribution and clearance of esophageal reflux, differentiating between the refluxate of liquid, gas, and combined liquid and gas. Swallowed or refluxed boluses change the resistance to current flow between pairs of the impedance

Figure 3: (a) Receiver operating characteristic curve for the best performing prespecified scoring method for Reflux Disease Questionnaire (RDQ) responses which assigned a negative value to responses on dyspepsia, compared with symptom-based diagnosis by family practitioners and gastroenterologists. (b) Receiver operating characteristic curve for the prespecified scoring method for RDQ responses, which added the scores of the heartburn and regurgitation items [69].

electrodes, with liquid boluses decreasing impedance while gas boluses increase impedance. This technology seeks to improve upon ambulatory pH monitoring by detecting reflux events regardless of their pH, measuring the amount of time refluxed material remains in contact with the esophageal mucosa and the distance above the LES to which the refluxate enters the esophagus [32].

The application of this technology has increased our understanding of the type, frequency, nature and extent of GER, adding dimensions that are not detected using ambulatory pH monitoring [33-35]. Studies in healthy individuals have shown that the majority of physiological reflux episodes are acid reflux [36-38]. Comparisons to patients with GERD have shown that overall reflux frequency (acid and non-acid) is higher than in healthy individuals [39,40]. In particular, patients with GERD have a higher frequency particularly of traditional acid reflux with weak acid reflux rather infrequent [41,42]. On the contrary, when treated with PPI, patients show a decrease in the occurrence of acid reflux, with no substantial change in the overall frequency of reflux events, due to a marked increase in the number of weak acid reflux [43]. The latter events appear to have a role in GERD symptoms, particularly in patients complaining predominantly of regurgitation, but their role is unclear for other symptoms [44]. Finally, impedance monitoring may help improve the accuracy of the correlation between reflux episodes ant the occurrence of symptoms (Symptom Index, SI), because it detects all episodes of reflux regardless of acid content [44]. A recently convened panel of 11 experts, the 'Porto Consensus', undertook an in-depth examination of the evidence surrounding the use of impedance monitoring as well as other diagnostic technologies and techniques in GERD diagnosis [45]. These experts concluded that "intraluminal impedance monitoring is the only recording method that can achieve high sensitivity for detection of all types of reflux episodes. Reflux is best detected by impedance and its acidity characterized by pH-metry". The role of pH-impedance recording seems to be at present the assessment of patients with a negative upper GI endoscopy, refractory to PPI therapy, in whom it remains to

be established whether acid reflux may still be the cause of persisting symptoms, whether functional heartburn of psychiatric conditions are the diagnosis, or whether non-acid reflux is the major player of complaints [46-48]. However, data on the role of impedance-pH in GERD management remains to date limited and further clinical trials are mandatory to assess it with accuracy [49,50].

Finally, recently, a minimally invasive device for detection of oropharyngeal acid reflux (Restech; Respiratory Technology Corp., San Diego, CA) was introduced that is well-tolerated and sensitive even to tiny droplets of acid. Preliminary findings suggest that this increases diagnostic yield of reflux as a cause of laryngopharyngeal symptoms [51]. However, its utility in the diagnosis and management of GERD has to be still investigated.

For a list of potential causes of PPI refractoriness see also (Table 2).

Symptom assessment

Heartburn and regurgitation are the cardinal symptoms of the disease [2]. Heartburn describes the sensation of discomfort or burning behind the sternum rising up to the neck, whereas regurgitation is the effortless return of stomach contents into the pharynx [4]. Patients often use the term heartburn to mean other upper gastrointestinal symptoms such as epigastric pain [7], so it is important to clarify this in the history. Curiously enough, in many languages in particular from Asia there is not a direct translation for the word heartburn [52]. In addition, symptoms often occur in clusters, and it can be difficult for the patient to define a predominant symptom [53]. Finally, symptoms such as dysphagia (cfr. above), odynophagia, pharyngeal globus, sore throat, laryngitis, water brash, and cough are other possible symptoms of GERD, but their diagnostic use is uncertain.

The accuracy of heartburn or regurgitation in the diagnosis of the disease is difficult to ascertain [4]. Some studies have suggested that the diagnostic use of these two symptoms is very useful [54], whereas other are more cautious [55]. In general, as shown also by a recent systematic review the sensitivity of reflux symptoms appears to be generally disappointing when endoscopy was used as a gold standard [56], with a range of 30% to 76% and a pooled sensitivity of 55% (95% CI 45% to 68%) (Figure 2). Thus, reflux symptoms are helpful in the diagnosis of the disease, but it is important to emphasize their lack of sensitivity; many patients with atypical upper gastrointestinal symptoms may have GERD.

It has been proposed that, at least in the setting of tertiary care or during a randomized controlled clinical trial, the use of GERD questionnaires may be useful. However, it is recognized that the development of such a GERD symptom assessment instrument has been hampered by some of the inherent clinical features of GERD [57]. For an example, an issue to be solved is which symptoms should be measured, in light of the wide variety of both "typical" and "atypical" GERD manifestations. Despite the fact that a number of tools have been proposed in the literature some of which present some features of the ideal GERD questionnaire [58], a valid, reliable, highly responsive, and easy to use assessment tool is at present lacking [57].

Finally, it is worth of noting that in some cases the clinical presentation as well as the diagnostic work-up of achalasia patients can show overlap with GERD [59]. Mistaking achalasia for GERD has to be avoided by esophageal manometry and this should therefore be performed in all patients undergoing surgical fundoplication.

PPI test

For many years it has been suggested that a pharmacological test, i.e., the so-called PPI (Proton Pump Inhibitor) test [60], might be useful for diagnosing GERD, particularly in the setting of primary care. The test consists of measuring the symptomatic response to a high-dose PPI treatment administered for 1 to 2 weeks in patients with GERD symptoms. The rationale for using short-term, high dose PPI administration as a diagnostic tool is based on the strong effect of PPIs on inhibition of gastric acid secretion, healing erosive esophagitis and improving GERD symptoms [61]. As far as the interpretation of the test is concerned, a positive response is usually considered on the basis of main symptom (ordinarily heartburn) improvement and cut-off values between 50% and 75% of symptom improvement have been claimed to provide the best diagnostic accuracy [62]. Since 1995, many studies have assessed the usefulness of this test in patients with typical GERD symptoms, with or without erosive disease; reported sensitivity values ranged from 27% to 89% and specificity values from 35% to 73% [63]. As the test aims at establishing that the patient's symptoms are acid-related, the dosage for the PPI test is higher than usual (in most studies, a double dose) in order to obtain a greater inhibitory effect on acid secretion 13 [64]. No definitive consensus about the duration of the PPI test has been reached; in most studies the duration is 7 to 14 days [20]. In 2004, Numans et al. [63] performed a systematic review and a meta-analysis of the value of the PPI test in diagnosing GERD in patients with typical symptoms. From the studies analyzed, these authors reported pooled sensitivity and specificity values of 78% and 54%, respectively, when compared to 24h pH monitoring, and 71% and 41%, respectively, when compared to upper GI endoscopy. They concluded that a successful PPI test in patients suspected of having GERD does not confidently establish the diagnosis when GERD is defined by the currently accepted reference standard. We designed a multicenter study in patients with typical GERD symptoms with or without erosive esophagitis [65], with the aim of assessing the usefulness of a short trial of high-dose PPI as a diagnostic test, and to determine (1) the optimal duration of PPI administration and (2) the best cut-off value of symptomatic response. Our study was specifically designed with the aim of assessing the clinical usefulness of PPI test as a confirmatory tool in a population of GERD patients with typical symptoms, and secondarily, the optimal duration of the test and the cut-off values of symptom response [65]. The results of the present study suggest that around 90% of our patients have a positive PPI test, according to the various thresholds used (Table 2). Based on the diagnostic operating characteristics and on the ROC analysis, the most useful cut-off value to define a positive response to PPI test is a symptom relief ≥ 75%, because it allows the maximal specificity value, while the optimal duration is 1 week, because sensitivity and specificity values are not different from those obtained after 2 weeks (Figure 3) [65].

The percentages of patients with a positive response, in our population, is higher than those reported in previous studies [38], and appears to be greater in EE than in NERD subjects, with a difference which reaches the statistical significance ($p < 0.05$) for the cut-off of 75% and the duration of 2 weeks (Table 2). While the sensitivity of the test according to the threshold used appears to be very good, ranging from 91.7% to 98.8%, and higher than than the maximal (89%) previously reported [41 diventa 66], specificity appears poor, ranging from 2.9% to 36.3% and comparable with the minimum reported value (35%) [66].

Discussion and Conclusion

Despite advances in diagnostic tests for GERD, a perfect diagnosis is probably impossible for many reasons, such as the heterogeneity of GERD manifestations and the lack of a gold standard. Also, it has long be recognized that no parallel exists between severity and frequency of GERD symptoms, for example, and presence or severity of esophageal mucosal lesions [67]. Thus, careful clinical history remains central to the evaluation of a patient with suspected GERD symptoms: most patients will have a relatively mild and non-life-threatening illness and in many instances a thoughtfully obtained history will lead to rapid and accurate management.

Alternatively, it is also important to identify patients who carry a higher likelihood of serious underlying disease so that they can be investigated and managed without any delay. Exhaustive diagnostic algorithm has been published for patients presenting ax an example with heartburn, chest pain, dysphagia or globus sensation and we will refer the reader to them [68]. However, the difficulty encountered in clinical practice in reaching a diagnosis of GERD is highlighted by the recent DIAMOND study [69], a study aiming at determining the accuracy of a symptom based diagnosis of GERD by using a symptom questionnaire (the RDQ) *vs.* an "informal" symptom-based diagnosis by family practitioners and gastroenterologists. The diagnostic value of a 2-week PPI test using esomeprazole 40 mg twice a day was also tested. Interestingly in the study, due to the lack of a single gold standard test for GERD, both endoscopy and wireless 48h pH recording with symptom association monitoring were used to provide an independent and objective reference standard for the diagnosis of reflux disease. The results of the study show that the sensitivity and specificity values for all the diagnostic tests used are rather disappointing, with percentages of the symptom-based diagnosis of GERD, were 62% and 67% for the RDQ questionnaire, 63% and 63% for family practitioners, and 67% and 70% for gastroenterologists, respectively (Figure 3). Symptom response to esomeprazole was neither sensitive nor specific for the diagnosis of GERD [69].

In conclusion, GERD remains an imperfect diagnosis which requires clinical skill, updated knowledge of newer technology, and appreciation of the wide spectrum of the clinical symptoms of this common disease.

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