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Special article

Exploring the spectrum of GERD: myths and realities

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SUMMARY

Concepts of the spectrum of gastroesophageal reflux disease (GERD) continue to evolve as researchers and clinicians challenge conceptual frameworks and explore new paradigms aided by innovative technologies and novel developments in symptom assessment. In this review, the deliberations of a meeting of experts in gastroenterology (Athens, 2006) are presented as a critical evaluation of the current understanding of GERD and its symptoms, and an exploration of future directions. Consensus statements from Genval, Marrakesh and Montreal present working definitions of GERD; these will, inevitably, continue to be refined as our understanding of the spectrum of GERD-associated symptoms evolves and our appreciation of differences among non-erosive reflux disease (NERD), erosive GERD and Barrett's esophagus, as well as the overlap between GERD and functional gastrointestinal disorders (FGIDs), grows. Currently, we lack an independent basis by which to determine whether particular symptoms are a manifestation of GERD per se or should be attributed to associated FGIDs. Furthermore our understanding of the etiology of atypical manifestations and extraesophageal symptoms is poor. It is possible that, in the future, acid-related NERD will become identifiable in terms of a microscopic inflammatory or ultrastructural change in the esophageal epithelium, thereby allowing a diagnosis of microscopic erosive reflux disease. It is likely that the natural history of GERD will be confirmed as largely benign and biomarkers will identify the minority who may be destined for a more sinister outcome. Finally, developments in symptom assessment will continue to improve our understanding of GERD and, ultimately, better predict treatment outcomes for patients.

Key Words: gastroesophageal reflux disease; GERD; symptom relief; PPI; ReQuestTM; functional gastrointestinal disorders; extraesophageal symptoms

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1. INTRODUCTION

The clinical spectrum of gastroesophageal reflux disease (GERD) continues to evolve as researchers and clinicians challenge currently held conceptual frameworks and explore new paradigms. GERD is now defined as a condition that develops when the reflux of gastric content causes troublesome symptoms, impairs quality of life (QoL), or leads to mucosal damage or complications.[1] This, Montreal, consensus is in general agreement with previous definitions[2,3] and permits a definition based on symptoms. In addition, the sub-classification of disease into esophageal and extraesophageal syndromes supports the growing agreement among clinicians that a large percentage of GERD patients suffers from a broad range of symptoms besides heartburn.[1] Nonetheless, despite this recognition of symptom diversity, the relationship of atypical and extraesophageal symptoms to GERD remains poorly understood, and there is a need to develop a clear understanding of the variety of symptoms that are truly associated with GERD.

The clinical picture is further complicated because symptoms in GERD overlap with those present in functional gastrointestinal disorders (FGIDs), such as functional dyspepsia (FD) and irritable bowel syndrome (IBS).[4-6] Currently, there is a need to determine if symptoms can be accurately and appropriately assigned to GERD or FGIDs and whether this is of any clinical value in determining assessment and management strategies. In addition, a greater understanding of the role of visceral hypersensitivity in the process of symptom pathogenesis may help to fur-

ther characterize FGIDs and non-erosive reflux disease (NERD). It is also essential to ensure that our definitions of NERD, erosive GERD and Barrett's esophagus are accurate; in this way, the current debate concerning whether GERD is a continuous spectrum or comprises distinct phenotypes may be resolved.

Finally, although acid suppression with proton pump inhibitors (PPIs) has provided high rates of esophageal mucosal healing and symptom relief in numerous clinical trials, almost half of patients with GERD on prescription medication have indicated that they are not satisfied with treatment.[7] This highlights a need to determine whether current measures of success and failure in the management of GERD are accurate and clinically relevant. In particular, it would be useful to better establish the extent to which findings obtained in clinical trials are representative of GERD treatment in daily clinical practice.

Experts in the field of gastroenterology gathered in Athens in 2006 to discuss these issues. The aim of the current review is to present conclusions from this meeting in the format of a critical evaluation of the current understanding of GERD, questioning the integrity of current dogma and exploring new concepts surrounding GERD and its symptoms (including assessment and diagnosis).

2. OVERLAP WITH FUNCTIONAL DISORDERS

Symptoms in patients with GERD overlap with those of other conditions, particularly FD and IBS. Data from both epidemiological and clinical studies show that 19–71% of patients with GERD report symptoms of IBS.[4] Lower abdominal/digestive complaints, often not thought to be associated with GERD, were bothersome to approximately 60% of patients with either NERD or erosive GERD in an analysis of the ReQuest™ database (Figure 1).[8] Conversely, the prevalence of GERD-related symptoms, such as heartburn, indigestion and bloating, was 33–75% among patients with IBS.[5] Furthermore, data from 22 studies showed a striking concordance, in a given patient, between upper abdominal pain and reflux symptoms, such that when the definition of dyspepsia was narrowed to exclude heartburn and regurgitation, its prevalence diminished dramatically.[6]

Mechanisms explaining these associations among functional gastrointestinal (GI) disorders remain poorly defined, although several common pathophysiological factors have been identified.[9] Also the induction of transient lower esophageal sphincter relaxations (TLESRs) in patients with GERD is primarily related to stimulation of mechanoreceptors in the proximal stomach; therefore, delayed gastric emptying or altered fundic accommodation may contribute to increased triggering of TLESRs.[10,11] Indeed, both impaired relaxation of the gastric fundus[12] and delayed gastric emptying have been commonly described among patients with FD.[13]

Visceral hypersensitivity appears to be an important underlying mechanism in FD, IBS and GERD, particularly in patients with NERD.[4,14] Defined as enhanced conscious perception of visceral stimulus independent of the intensity of the stimulus, visceral hypersensitivity involves both peripheral and central mechanisms. Visceral perception may be amplified in patients with FGIDs or GERD through either peripheral sensitization, which could be due to acid exposure, or other injuries causing micro-inflammation and other molecular changes, whereby there is a reduction in the threshold of the primary terminals of nociceptive primary afferents, or central sensitization, resulting from an

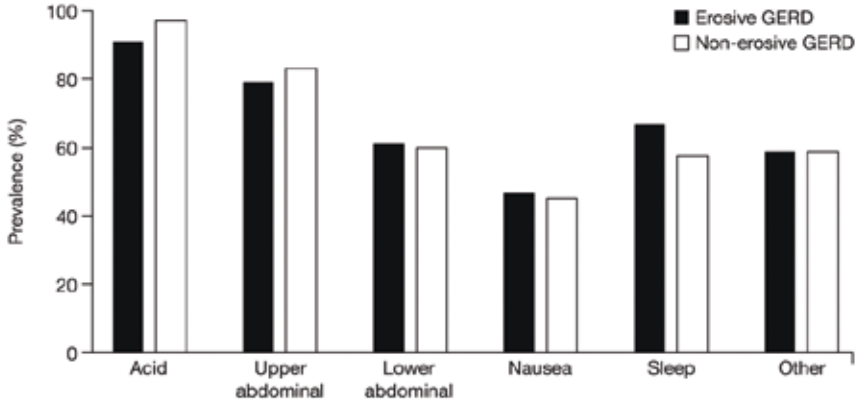

Figure 1. Symptom patterns in gastroesophageal reflux disease (GERD). Results from the ReQuest™ database showing percentage of patients with symptoms at baseline (per protocol population, n= 6810)

increase in the excitability of spinal neurones induced by afferent signals from nociceptive fibers activated at the injured site.[15,16] Output throughout the central nervous system may be amplified through the convergence of multiple sensory afferents onto the dorsal horn neurones.[15,17]

3. ATYPICAL MANIFESTATIONS AND EXTRAESOPHAGEAL SYMPTOMS

Previously, GERD has been characterized by the symptoms of heartburn and acid regurgitation; however, it has also been associated with several atypical manifestations and extraesophageal symptoms (e.g., asthma, chronic cough, non-cardiac chest pain [NCCP] and laryngitis) (Table 1).[18,19] Whereas a plausible rationale for the induction of these manifestations by reflux can be advanced, it is now clear that GERD-associated extraesophageal symptoms may not be as prevalent as previously thought. Indeed, in many instances, associations between GERD and these manifestations are difficult to establish. Furthermore, our current understanding of the etiology of these symptoms is poor.

Several pulmonary conditions have been associated with GERD, the most common being asthma – with up to 80% of patients with asthma experiencing heartburn.[18] However, a cause-and-effect relationship between the two conditions is difficult to establish, and there are currently no gold standard diagnostic techniques for assessing such a relationship. Causality cannot be established by treatment studies showing improvement of heartburn and asthma because of the complicating issue of placebo response, nor can it be deduced from prevalence studies showing an association between the two conditions, as either may cause the other. Acute asthma episodes may result in the reflux of gastric contents into the esophagus by creating a negative intrathoracic pressure, or GERD may induce asthma, either directly by micro-aspiration or, indirectly, by stimulation of vagal afferents in the distal esophagus.[18] The clinical picture is further complicated by multi-causality.

Combined with a poor understanding of the etiology of extraesophageal symptoms, difficulties in diagnosis have led to treatment algorithms that are based on rather limited knowledge.[18] For example, PPI therapy twice daily for 1–2 months is recommended in patients with atypical or extraesophageal symptoms.[18] However, with few exceptions,[20] there has been scant evidence of any benefit for acid suppression with PPIs over placebo among patients with ear, nose and throat (ENT) symptoms or laryngitis from either clinical trials[21-24] or meta-analyses.[25] Nonetheless, these findings are unlikely to represent PPI failure but rather reflect our inability to identify the subset of patients for whom treatment will be beneficial. For example, reflux laryngitis is commonly diagnosed on the basis of the laryngoscopic findings of edema or erythema; however, these are highly subjective measures and have shown poor specificity for GERD.[26] Other laryngeal signs (e.g., contact ulcers or granuloma) represent a more objective measure, but these may also be observed in healthy individuals secondary to smoking, excessive alcohol use, allergies, asthma or viral illnesses.[26] Finally, although hypopharyngeal pH monitoring has been advocated in patients with ENT signs and symptoms, a positive test does not predict response to acid-suppressive therapy.[26]

4. CHANGING NATURE OF GERD

As discussed above, making a diagnosis of NERD is challenging given the considerable overlap with FGIDs, along with the lack of clinical features or criteria on pH study or histology that would allow for the clear identification of this condition.[27] Recent technological developments have demonstrated that NERD is not a homogeneous condition, and patients may have: (1) abnormal acid exposure;

Table 1. Atypical manifestations and extraesophageal symptoms in patients with gastroesophageal reflux disease (GERD)[18,19]

Dyspepsia & IBS	Ear/Nose/Throat	Pulmonary	Cardiac	Other	Sleep
• Epigastric pain • Nausea • Upper abdominal discomfort • Lower abdominal discomfort • Belching • Bloating • Stool alterations	• Laryngitis • Sinusitis • Otitis • Granuloma • Polyps • Laryngeal carcinoma • Hoarseness, throat clearing, globus, sore or burning throat	• Asthma • Chronic cough • Pneumonia • Bronchitis • Interstitial fibrosis	• Chest pain • Sinus arrhythmia	• Dental erosions • Halitosis	• Sleep quality

IBS, irritable bowel syndrome.

(2) normal acid exposure and symptom correlation; (3) normal acid exposure and no correlation between reflux and symptoms. The first two groups may have microscopic erosive reflux disease (ERD), i.e., minimal changes to the esophagus (such as dilation of intercellular spaces) that can be identified using histology, high resolution magnifying endoscopy and/or electron microscopy.[27-31] Thus, it is conceivable that acid-related NERD will be redefined in the future as microscopic ERD. However, for the present, neither the sensitivity nor the specificity of microscopic change has been shown to closely match reflux indices, and improved diagnostic performance of microscopic techniques is awaited.[31]

The third group of patients, commonly referred to as functional heartburn, remains problematic. An early study in a group of patients (not all had functional heartburn) with persistent heartburn despite full-dose PPI therapy showed that some had abnormal acid exposure (i.e. truly had acid reflux) and others had abnormal exposure to other components of the refluxate, raising, yet again, the possibility that bile, digestive enzymes or other intestinal contents may be relevant to symptom generation.[32] Other mechanisms of symptom production in these individuals may include abnormal tissue resistance, visceral hypersensitivity or sustained esophageal contractions. Fass and Tougas suggest that symptom production in functional heartburn is through an interaction of luminal stimuli, central factors and local reflexes, the primary initiating factor being acid exposure.[33]

Although there is variation, it is likely that the natural history of GERD will be confirmed as largely benign.[34,35] Very few patients with GERD progress to more severe disease. Rather, in the majority of patients, disease status after long-term treatment is generally the same as that at baseline.[34,35] However, it is evident that patients with Barrett's esophagus have a higher risk of progression to adenocarcinoma than the general population, thus suggesting that the diagnosis of Barrett's esophagus continues to be important,[36] although it remains to be shown that the incidence and mortality of Barrett's adenocarcinoma can be reduced by clinical intervention. Data from a multivariate logistic regression analysis demonstrated that family history was independently associated with the presence of Barrett's esophagus, esophageal adenocarcinoma, or esophagogastric junctional adenocarcinoma (odds ratio: 12.23, 95% confidence interval: 3.34–44.76), suggesting that a positive family history for Barrett's esophagus should be considered when screening for the disease.[37] In the future, it is likely that biomarkers will identify the minority of patients who are most likely to be at greatest risk of malignancy, enabling better targeting of measures to prevent cancer development.

5. DIAGNOSIS AND ASSESSMENT OF GERD

5.1. Diagnosis

The initial diagnosis of GERD is usually based on symptom assessment combined with the response to empirical treatment with a PPI. The PPI test, however, remains less than ideal for the accurate diagnosis of GERD.[38] Available data show that the sensitivity and specificity of the test are highly variable (0.38–0.79 and 0.21–0.71, respectively) as are the positive and negative predictive values (0.17–0.90 and 0.17–0.91, respectively). Such disappointing results may be explained, in part, either by the inadequacy of the comparators used (e.g., endoscopy, 24-hour pH testing or symptom assessment) or by the inability of acid suppression to differentiate between GERD and peptic ulcer disease or dyspepsia.[38] There is also currently no consensus on what PPI dose or duration of administration constitutes an appropriate test.

Endoscopy should be reserved for patients with an uncertain diagnosis, alarm symptoms, or those not responding to PPI therapy. When the diagnosis of GERD is uncertain, 24-hour esophageal pH monitoring may help to determine whether the patient's symptoms are due to reflux. This test is especially appropriate when endoscopy has not revealed the presence of mucosal lesions.[39,40] Esophageal pH monitoring should quantify esophageal acid exposure during the recording period (percentage of time with pH<4) but should also seek to determine the strength of association between symptoms and acid reflux events (expressed as symptom index [SI] or symptom association probability [SAP]).[39,41] In patients with persistent symptoms despite acid-suppressive therapy, conventional 24-hour esophageal pH monitoring could be done after the PPI has been discontinued. However, this is usually not helpful in patients receiving a PPI, and it does not detect all gastroesophageal reflux events when there is little or no acid present in the refluxate.[39,40]

Non-acid reflux is best measured using esophageal bilirubin absorbance monitoring (Bilitec) or intraluminal esophageal impedance recordings.[39] The biggest contribution of impedance is in symptom–reflux association analysis, particularly in patients receiving PPI therapy. Impedance can be used alone or in combination with pH-metry and manometry.[40] When combined with pH monitoring, it is useful for detecting all reflux events, distinguishing between acid, weakly acidic and non-acid reflux, and assessing the duration and/or proximal extent of a reflux event,[40]

thereby helping to define the origin of persistent symptoms in patients with GERD on PPI therapy.[42] Impedance combined with manometry (which can detect cough events) is useful in identifying reflux as the cause of symptoms in patients with unexplained chronic cough.[43] However, the widespread application of impedance monitoring is hampered by the need for careful and time-consuming inspection of signals. Furthermore, additional data from appropriately designed clinical trials is needed to demonstrate an impact on patient outcome.[39]

Magnetic resonance imaging (MRI) provides a simultaneous structural and functional assessment of the GI tract that is non-invasive and free of ionizing radiation.[44,45] It allows for the measurement of gastric motility and emptying and has been proposed as a technique for measuring gastric accommodation.[45] It is likely to be more acceptable to the patient and physician than more invasive techniques. However, the role of MRI in the assessment of GERD has yet to be fully established and the availability of MRI equipment for this purpose is likely to be limited in some clinics.

5.2. Assessment of treatment response

Traditionally, the primary outcome criterion in clinical trials has been healing of esophagitis. However, this is not an appropriate endpoint for the majority of patients with GERD who do not, after all, have esophagitis at the outset,[46-49,47] and a strong argument can be made for the evaluation of both symptom relief and improvements in QoL in assessing the response to treatment. Indeed, many patients with symptoms such as heartburn and acid regurgitation, do not have excessive acid reflux.[50] Furthermore, patients with excessive acid reflux commonly report a broad range of esophageal and extraesophageal symptoms, which will not be captured by an evaluation confined to the "classical" symptoms.[1,50,51] Finally, symptom relief is of primary importance to patients, and the impact of GERD on QoL depends on the severity of symptoms rather than the degree of mucosal injury.[47,48]

Nonetheless, there has previously been no gold standard for evaluating symptoms in a clinically meaningful way and there are substantial variations in outcome criteria in clinical trials.[52] Until recently, symptom evaluation has generally been restricted to an assessment of one, or at most two, symptoms and is usually confined to a single symptom: heartburn.[52] This approach has not taken into consideration the broad spectrum of GERD-associated symptoms (e.g., atypical manifestations and extraesophageal symptoms) or associated disorders (e.g., IBS and dyspepsia). The assessment of these is important because heartburn may be non-dominant or even absent among some patients with excessive reflux or erosive reflux disease,[19] additional upper GI symptoms may respond less predictably to therapy than does heartburn,[53] and underlying (and perhaps more "classical") symptoms may not be fully perceived until the predominant symptoms are relieved.[52] In addition, the definition of treatment success varies across clinical trials and may include either the complete absence of a symptom or a subjective reduction in symptom severity (or intensity) and/or frequency. In clinical trials, symptom evaluation is usually carried out at pre-defined and fixed time points, often at 4 or 8 weeks following treatment initiation. This approach fails to take into account the episodic nature of symptoms and day-to-day variations in symptom severity and duration resulting from changes in diet, exposure to stressors or medication use.[52] Finally, assessment is often performed from the perspective of the physician or investigator, which can differ significantly from that of the patient.[54] Although there are advantages and disadvantages to each perspective, the patient's perspective may be more relevant when evaluating treatment response because it is the patient who experiences the symptoms, thereby suggesting that self-assessment is more accurate.[52]

Thus, symptom assessment during the course of treatment should ideally be carried out using a tool that considers both typical and atypical symptoms, covers all symptom dimensions, is valid in patients with either NERD or erosive GERD, and is sensitive and rapidly responsive to symptom changes.[52] In addition, it should, for international use, be valid in different languages, be economical and practical, patient-assessed, suitable for daily use,[52] and have proven validity, reliability and responsiveness in clinical trials. Several symptom assessment questionnaires and QoL scales have been used in clinical trials, but, until recently, none fulfilled all criteria for the ideal symptom assessment tool (Table 2).[55,56]

Among the most recently developed questionnaires, ReQuest™ provides a statistically valid assessment of the broad range of GERD-associated symptoms in patients with erosive GERD and NERD.[57-59] It enables the sensitive tracking of symptom changes on a daily basis and provides a simple, fast and convenient way to measure both the frequency and intensity of symptoms.[57-60] ReQuest™ exists in both a short and long version, each comprising seven dimensions of GERD, which are divided into two validated subscales: ReQuest™-GI, including the dimensions of nausea, acid-related complaints, and upper abdominal/stomach and lower abdominal/digestive complaints, and ReQuest™-WSO, which covers general wellbeing, sleep disturbances, and other complaints.[59,61] Symptom intensity is measured

Table 2. Characteristics of symptom assessment tools for GERD[56]

Instrument	GERD-specific	Validation	Multiple dimensions	Self-assessed	Daily assessed	Different languages
ReQuestTM	+	+	+	+	+	+
GERD Score	+	+				
UESS		(+)*	+	+		
GSAS	+	+	+	+		
GSRS		+		+		+
GRACI	+	+V,R	+	(+)*	(+)*	
GSFQ	+	+		+		
GERDQ	+	+	+	+		
RDQ	+	+	+	+		
GERD assessment scale	+	+	+	+		
PAGI-SYM		+	+	+		+
FSSG	+	(+)*	+	+		Japanese English/ French
PASS-Test	+	+		+		
Symptom diary	+			+		

(+) Only parts of the scale.*
UESS, Ulcer Esophagitis Symptoms Scale; GSAS, GERD Symptom Assessment Scale; GSRS, Gastrointestinal Symptom Rating Scale; GRACI, Gastroesophageal Reflux Disease Activity Index; GSFQ, GERD Symptom Frequency Questionnaire; GERDQ, Chinese GERD Questionnaire; RDQ, Reflux Disease Questionnaire – Germany Version; PAGI-SYM, Patient-assessed Upper Gastrointestinal Symptom Severity Index; FSSG, Frequency Scale for Symptoms of GERD; PASS-Test, PPI Acid Suppression Symptom Test.
V, variability; R, reliability.
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on a 100-mm visual analogue scale and frequency (except well-being) is measured on a 7-point Likert scale.

Symptom relief is achieved when the score on the ReQuest™-GI subscale falls below a predefined upper limit on the GERD symptoms threshold.[61] The use of such a threshold is essential given that individuals without evidence of GERD may experience mild symptoms that are commonly ascribed to the disease. This concept allows for the assessment of novel parameters, such as the first time to symptom relief and the time to sustained symptom relief (Figure 2),[61] and allows for the detection of treatment differences among PPIs.

In order to combine the assessment of symptom relief with endoscopic healing of esophageal lesions, the com-

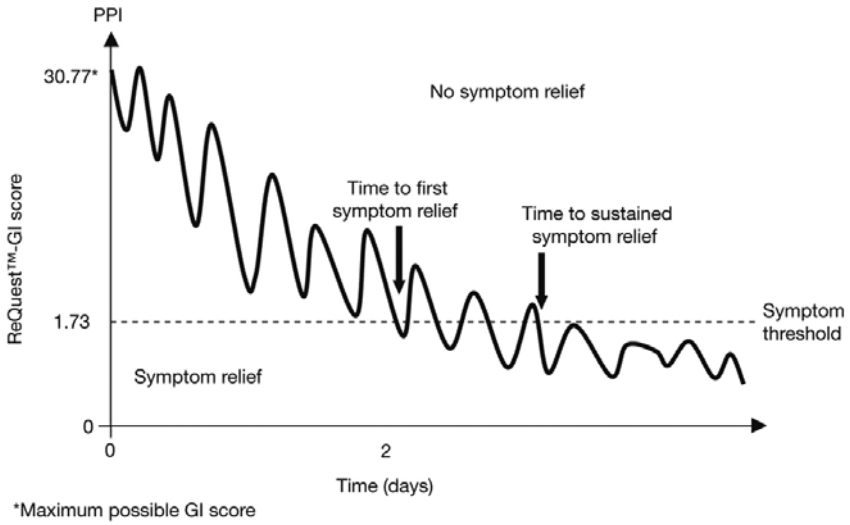

Figure 2. Threshold concept: assessment of response to treatment showing time to first and sustained symptom relief

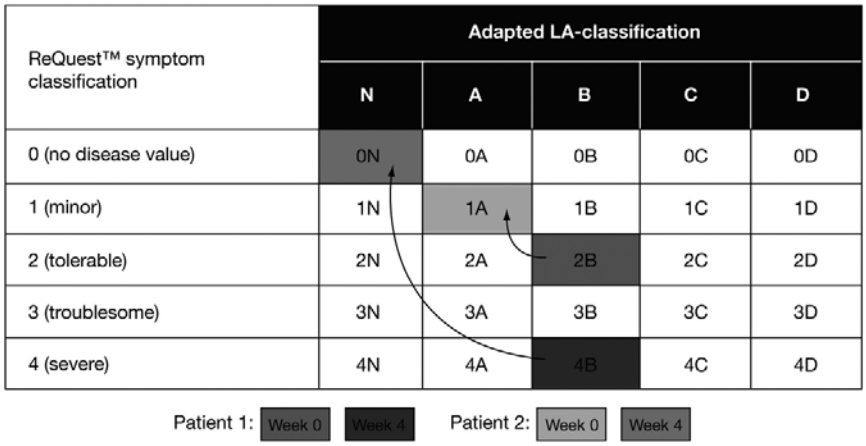

Figure 3. The combined ReQuest™/LA-classification

plete remission concept, which integrates ReQuest™ and an adapted version of the Los Angeles (LA)-classification, was developed.[55] In this measure, the ReQuest™-GI score was rescaled to establish categories of symptom burden according to the patient's perceived impairment of well-being (0=no disease value, 1=minor, 2=tolerable, 3=troublesome, and 4=intense), and an adapted version of the LA-classification (N=not present, LA grade A–D) was used. Complete remission is achieved when a patient is classified as 0N, i.e., symptoms have been relieved and there are no endoscopically detectable erosions (Figure 3). Combining the categories of symptom burden with the adapted LA-classification provides a quantitative evaluation of the complete symptom spectrum in patients with GERD, permits monitoring the course of disease in individual patients, provides an adequate assessment of all clinically relevant therapeutic outcome parameters, and offers the possibility of uniform reporting in clinical trials, thereby providing comparability.[55] Findings from the complete remission study indicate that the total remission of symptoms – determined by ReQuest™ and calculations based on the threshold concept – is a strong predictor of endoscopic healing; if symptoms are suppressed to below the threshold level, there is a 90% probability of the patient being healed.

6. CONCLUSION

Although our understanding of GERD and its associated symptoms is developing, data and expert opinion presented at a recent educational meeting in Athens demonstrate that conceptual paradigms will continue to evolve aided by developments in diagnostic techniques, symptom assessment instruments and innovative research. Our current state of knowledge suggests that although there is an overlap between GERD, FD and IBS that is likely to be explained by common underlying pathophysiological mechanisms, we currently do not have valid means by which to determine whether a symptom is due to this overlap or is a manifestation of GERD per se. This presents a difficulty for identifying the symptoms that may be expected to respond to GERD treatment. Our understanding of the etiology of extraesophageal symptoms is poor and management problematic. In the future, it may be possible to determine a subset of patients for whom specific treatments will be beneficial. It remains essential to clearly define reflux disease, although the published consensus statements from Genval,[2] Marrakesh[3] and Montreal[1] are in substantial agreement and at present can be accepted as working definitions of GERD, both in research and in clinical practice. In the future, it is possible that acid-related NERD will be identifiable in terms of microscopic inflammatory change in the esophageal epithelium, such that a diagnosis of microscopic erosive reflux disease may be made. It is likely that the natural history of GERD will be confirmed as largely benign and biomarkers will identify the minority of patients who are most likely to have a less benign disease course. Recent developments in diagnostic techniques and instruments for symptom assessment together with a recognition of the need to treat both lesions and symptoms will continue to improve our understanding of GERD and ultimately treatment outcomes for patients.

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