

Endoscopy of the esophagus in gastroesophageal reflux disease: are we losing sight of symptoms? Another perspective

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SUMMARY. Gastroesophageal reflux disease (GERD) is an extremely common chronic disorder associated with impaired quality of life and huge economic burden. Recently, an International Consensus Group developed a global definition of GERD (The Montreal Definition): a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. The traditional endoscopy-based classification of GERD patients into one of three groups – non-erosive reflux disease, erosive esophagitis, and Barrett’s esophagus – is fraught with several limitations. Due to the lack of a gold standard, GERD is a symptom-based diagnosis, and hence symptom evaluation will remain the primary means by which treatment decisions are made for patients with suspected GERD. We propose that patients reporting the predominant GERD-like symptoms (GERS) in the primary care setting be classified based upon their response to an empiric trial of acid suppressive therapy: complete response to acid suppressive therapy, partial response to acid suppressive therapy, and no response to acid suppressive therapy. Given the limitations of objective medical testing, implementation of our proposed new symptom-based classification of patients with GERS would guide primary care physicians on when to refer patients to a gastroenterologist, which in turn could help in better resource utilization. Validation of this proposed classification by well-designed prospective multicenter studies is awaited.

KEY WORDS: Barrett’s esophagus, endoscopy, erosive esophagitis, gastroesophageal reflux disease, non-erosive reflux disease.

BACKGROUND AND SIGNIFICANCE: REFLUX SYMPTOMS AND ESOPHAGITIS

Gastroesophageal reflux disease (GERD) is an extremely common chronic disorder in Western countries.^{1,2} It affects 20–50% of adults in developed countries, and approximately 25 million adults in the USA experience heartburn daily.^{3–5} In addition, GERD significantly decreases quality of life (QOL) and is responsible for higher medical costs than any other gastrointestinal disease in the USA.^{2,6–9}

Recently, an International Consensus Group developed a global definition of GERD (The Montreal Definition): a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.¹⁰ Gross evidence of esophageal injury due to GERD includes erosive or ulcerative esophagitis, stricture, Barrett’s esophagus (BE), and esophageal adenocarcinoma.¹⁰ It is estimated that 40–50% of patients with typical reflux symptoms in tertiary centers and only 20–30% in primary care practice have erosive esophagitis.¹¹ BE is estimated to be present in 10% of patients with long-standing GERD. Although these patients are routinely enrolled in surveillance programs, the overall risk of cancer in BE patients is low (approximately 0.5% per year). Clinical complications of hemorrhage or stricture occur in approximately 1% of patients with GERD.¹² Thus, complications with GERD are infrequent and for the vast majority of patients,

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symptoms and their effect on QOL is the only parameter for assessing the impact of this disease. What differentiates the presence of gastroesophageal reflux symptoms from GERD is not clear and when the term 'disease' is applied to the patient.

Given the lack of a gold standard in the diagnosis of GERD and the limitations of objective testing, the authors make a case for symptom evaluation as the primary means by which treatment decisions should be made for patients with suspected GERD. We propose a symptom-based classification that incorporates patient response to acid suppressive therapy.

GERD SYMPTOMS AND QOL

Studies have shown that health-related quality of life (HRQOL) is reduced in GERD patients (in both erosive esophagitis and non-erosive reflux disease [NERD] groups) and experiencing heartburns at least twice a week is thought to be sufficient to result in impaired HRQOL.⁹ Several generic (e.g. Psychological General Well-Being Index [PGWBI], 36-item Short-Form Health Survey [SF-36]) and disease-specific (e.g. Gastrointestinal Symptom Rating Scale [GSRS], GERD-HRQL) HRQOL instruments have been applied to patients with GERD.

These studies emphasize that it is the severity of the symptoms rather than the presence or severity of the endoscopic mucosal damage that accounts for the adverse impact on HRQOL and productivity of GERD patients. There is substantial evidence that proton pump inhibitors (PPIs) lead to the resolution of symptoms and in turn improve HRQOL, an effect that occurs regardless of whether esophagitis is present or not. Therefore, it is surprising that the presence of erosive esophagitis is often perceived as a reflection of the severity of the disease.

CLASSIFICATION OF GERD: THE FOCUS ON ENDOSCOPY

Traditionally, GERD patients have been categorized into one of three groups: NERD, erosive esophagitis, and BE, based on the findings of an upper endoscopy.¹³ This endoscopy-based classification is fraught with several limitations. The majority of GERD patients show no signs of esophagitis by endoscopy, thus, making standard endoscopy an insensitive test for the diagnosis of GERD.¹⁴⁻¹⁶ Also, patients classified as NERD have a similar range of symptoms with erosive esophagitis and an impact on QOL at least comparable to that of erosive disease.¹⁶ However, in clinical practice, symptoms do not reliably differentiate between NERD and erosive esophagitis. It is also not clear whether NERD patients have been partially

treated and originally had erosive esophagitis. Furthermore, accurate evaluation and management of NERD patients is obscured by the inclusion of patients with functional heartburn and hypersensitive esophagus.^{17,18} Most studies involving patients with NERD do not document the cause of the GERD-like symptoms (GERS) and represent a mixture of patients with classic acid reflux along with a variety of other pathogenetic mechanisms to explain their symptoms. Inclusion of patients without acid reflux in studies of NERD are most likely responsible for the low response rates of NERD patients to PPI therapy, quoted frequently in the literature.¹⁹ The management conundrum in NERD patients is compounded by the overlap of symptoms of functional dyspepsia and irritable bowel syndrome.²⁰ Thus, NERD is not an appropriate label for these patients because it includes individuals with GERS resulting from acid reflux, non-acid reflux, or factors unrelated to gastroesophageal reflux. Moreover, irrespective of the diagnosis of erosive esophagitis or NERD, all patients with symptoms suggestive of reflux are initially given a trial of acid suppressive medication.

Because we currently have no simple laboratory test or diagnostic procedure which can consistently distinguish between those with reflux and those with symptoms resulting from conditions unrelated to reflux, GERD remains a symptom-based diagnosis; hence, symptom evaluation will remain the primary means by which primary treatment decisions are made for patients with suspected GERD. A shift in our thinking and management of GERD from an endoscopy-based to a symptom-based approach is essential. Recently, an International Consensus Group developed a global definition and classification of GERD using rigorous methodology. There was a conceptual change in the classification of GERD-related manifestations in which it was presented as a set of syndromes. The definition allowed asymptomatic patients with complications such as BE to be included in the case definition of GERD, and be independent of technology used to achieve a diagnosis.¹⁰

We wish to distinguish between endoscopy performed to diagnose and manage GERD and the 'once-in-a-lifetime' endoscopy recommended in patients with chronic GERD symptoms to screen for BE. The screening examination is not performed to diagnose erosive versus non-erosive GERD or to direct the management of the patient's GERD.

Primary care physicians and other specialists frequently prescribe acid suppressive therapy. This coupled with the recent availability of omeprazole without a prescription, has made the referral of *de novo* reflux patients to the gastroenterologist largely a thing of the past. An overwhelming majority of patients with heartburn seen in the referral setting have not adequately responded to PPI therapy. The

endoscopist cannot determine whether or not the patient previously had esophagitis that has already healed. This blurs the line between patients with NERD and erosive esophagitis, and potentially leads to misdiagnosis of patients. The endoscopy-based classification also does not identify nor establish a management plan for those patients who either have a partial response or fail acid suppression therapy.

In addition, there is no evidence that persistence of erosions in patients without GERD symptoms or in patients that are on acid suppressive therapy in whom symptoms have been resolved increases the risk of complications such as peptic strictures, BE, or esophageal adenocarcinoma. The Kalixanda study report estimated the prevalence of gastroesophageal reflux symptoms and erosive esophagitis in the adult population of two Swedish municipalities, 40% reported GERD symptoms and erosive esophagitis was found in 15.5% of the population that underwent upper endoscopy. Interestingly, 36.8% of those with erosive esophagitis reported no GERD symptoms.¹⁵ The prognostic implication of asymptomatic erosive esophagitis is unknown.

A CLINICAL, PRACTICAL CLASSIFICATION: FOCUS ON GASTROESOPHAGEAL REFLUX SYMPTOMS

Given the limitations of objective diagnostic testing, assessment of GERS, which can be accomplished with a structured patient interview or patient-completed questionnaire, is central to the diagnosis of GERD. Diagnosis and pretreatment severity assessment rests heavily on symptom evaluation, as do assessments of treatment outcomes. Yet, there is a paucity of data on the specific structure and content of the symptom evaluation which maximizes its diagnostic value.

A number of validated GERD questionnaires have been developed. When compared to structured interviews by health-care providers, questionnaires offer a number of potential advantages including lower interobserver variability, greater efficiency, reduced expense, and the ability to quantitatively assess the individual's response.²¹ However, these questionnaires are primarily diagnostic and may not adequately assess for changes in GERD symptoms and HRQOL following therapy. To bridge this gap, a new scale was developed and validated internationally in studies involving GERD patients—the Reflux Questionnaire. This self-assessed, dimension-oriented scale has been shown to be reliable and highly responsive for the daily assessment of changes in GERD symptoms and thus, acceptable as a primary outcome measure for clinical studies that are designed to assess the effect of treatment on the spectrum of GERD symptoms.^{22,23} Development of such a questionnaire that can be used in daily clinical practice is highly

desirable but remains to be achieved. At the current time, the use of questionnaires in GERD remains largely confined to the research arena.

Given the various limitations of an endoscopy-based classification and the lack of a simple validated questionnaire intended for use in clinical practice, a simple symptom-based classification system would be of considerable benefit to the initial management of patients reporting GERS. Given the safety and effectiveness of acid suppressive therapy, a trial of acid suppression has become standard practice in patients with reflux symptoms, irrespective of whether endoscopy has been performed or whether erosive disease has been documented. A number of studies have shown that patients can be adequately managed using an empiric trial of PPIs. In empiric trials of GERD, the relative risk for the resolution of heartburn with PPI therapy as compared to placebo was 0.37 (95% confidence interval [CI]: 0.32–0.44), and PPIs were significantly better than H₂-RAs (relative risk 0.66, 95% CI: 0.60–0.73).²⁴ Current clinical guidelines support empirical therapy in GERD and recommend a trial of standard dose PPI therapy for 1–2 months in standard dose.^{25,26} This strategy may also be the most cost-effective way of managing patients with reflux symptoms.

We propose that patients reporting predominant GERS in the primary care setting be classified based upon their response to an empiric trial of acid suppressive therapy for 2–8 weeks (Fig. 1):

- 1 Complete response to acid suppressive therapy (GERS-C).
- 2 Partial response to acid suppressive therapy (GERS-P).
- 3 No response to acid suppressive therapy (GERS-N).

GERS-C includes patients with complete relief of heartburn and/or regurgitation, GERS-P is defined as presence of troublesome reflux symptoms although reduced in intensity and/or frequency from baseline (an improvement of at least 50%) and GERS-N as minimal or no relief of reflux symptoms. This classification takes into account partial responses rather than the more absolute end points usually employed in GERD studies. Assessing response as early as 2 weeks was chosen based on the multicenter, randomized, double-blinded controlled study that assessed response to intermittent treatment in patients with symptomatic GERD. The most important prognostic factor was the response to initial treatment; patients with no symptoms at the end of 2 weeks of treatment had better outcomes.²⁷

Currently, the optimal endpoint for symptom relief is unknown. Many patients appear to be satisfied with less than complete symptom resolution. For example, in a double-blind trial of PPI therapy, 66% of patients reported 'sufficient' heartburn control, but only 46% had absence of symptoms over a 7-day

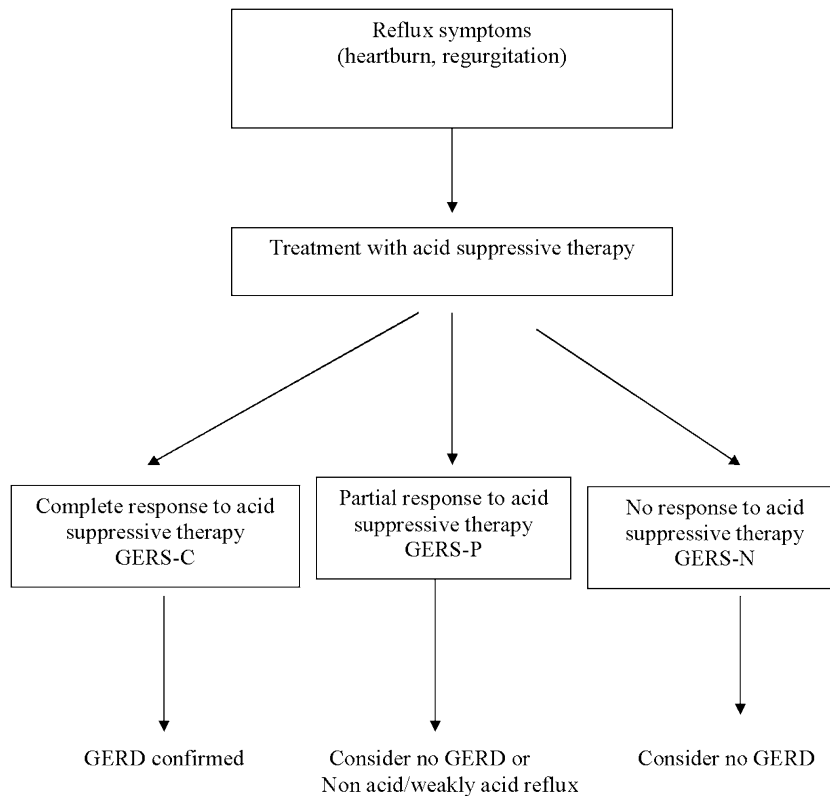


Fig. 1 Proposed classification for patients with gastroesophageal disease (GERD)-like symptoms (GERS).

assessment period.²⁸ Similarly, a systematic review that evaluated heartburn resolution in NERD patients showed that higher proportion of patients achieved sufficient heartburn resolution compared with complete heartburn resolution.²⁹ Future clinical trials need to focus on patient-centered goals regarding the effectiveness of therapy. Such outcomes are also influenced by a number of factors including gender, cultural background, psychosocial characteristics, and baseline severity of symptoms. It should be noted that this classification does not take into account the utility of other interventions for GERD such as dietary/lifestyle measures, endoluminal, or surgical interventions. Also, this classification is not designed to assess the severity or impact of symptoms on HRQOL. The other important caveats that should be borne in mind include the fact that a significant proportion of patients with esophageal adenocarcinoma do not perceive reflux, presence of symptoms in patients with irritable bowel syndrome, non-ulcer dyspepsia, and esophageal hypersensitivity and lastly, the placebo effect that cannot be ignored. The initial symptom assessment should include a comprehensive screen for alarm symptoms (weight loss, dysphagia, etc) and, if identified, prompt endoscopy is indicated. Based on the proposed classification, patients with GERS-N and GERS-P should be referred to a gastroenterologist for further evaluation.

This approach should not be confused with the PPI test (a rapid symptomatic response to normal-dose PPIs in patients with a presumptive diagnosis of GERD that has, until recently, been considered to validate the diagnosis). Available evidence suggests that the utility of the PPI test in diagnosing GERD is limited. A recent meta-analysis assessed the diagnostic test characteristics of the PPI test in comparison to 24-hour pH monitoring, endoscopy findings, and symptom questionnaires.³⁰ With 24-hour pH as the reference, the positive likelihood ratio ranged from 1.63 to 1.87 and combined estimates of sensitivity and specificity were 78% (95% CI: 66–86) and 54% (95% CI: 44–65), respectively. A poor correlation between the PPI test and endoscopic findings and symptom questionnaires was noted. These results likely underestimate the presence of GERD due to the lack of a true diagnostic gold standard and limitations inherent to the reference standards used in this analysis. As per this analysis, 20–40% of patients who have GERD on the basis of objective testing may not exhibit a response to a short trial of PPI.³¹ The focus on patient-centered goals regarding effectiveness of acid suppressive therapy and categorization of patients into groups based on degree of response to acid suppressive therapy is the most important difference between the proposed classification and the PPI test. It is easy to lose sight of the fact that the

presence of objective abnormalities on pH testing or endoscopy in patients with symptoms such as heartburn or chest pain does not prove cause and effect. It may well be that in some patients; the response to PPI therapy may provide a better reflection of whether symptoms are the consequence of GERD than the results of objective tests such as endoscopy, pH or impedance testing. This remains yet to be proven in appropriately designed clinical studies.

APPLICATION AND IMPACT OF THE NEW CLASSIFICATION SYSTEM

The Montreal classification of GERD divided the manifestation of GERD into esophageal and extraesophageal syndromes, with extraesophageal syndromes divided into established and proposed associations. Uninvestigated patients with esophageal symptoms but without evidence of esophageal injury are considered to have esophageal symptomatic syndromes while patients who do have demonstrable injury are considered to have esophageal syndromes with esophageal injury. This classification allows symptoms to define the disease but permits further characterization if mucosal injury is found. The term NERD or endoscopy negative reflux disease was not used in the classification scheme as they are based entirely on endoscopy findings, which may not be utilized in many patients and which is likely to evolve with new diagnostic modalities.¹⁰ Unfortunately, the above classification does not account for the response to acid suppressive therapy.

Thus, symptoms play a central role in the diagnosis of GERD. Given the limitations of objective medical testing, implementation of our proposed new symptom-based classification of patients with GERS could potentially lead to reduced costs with improved care. Cost-effective analysis should be performed if this proposed classification is proven to be effective in large well-conducted trials. This simple symptom-based classification allows clinicians to focus on GERS (and if present other symptoms such as dyspepsia and bloating that frequently co-exist with GERS), takes into account the changing patterns of the condition and response to acid suppressive therapy. This classification would guide primary care physicians on when to refer patients to a gastroenterologist, which in turn could help in better resource utilization and reduction in unnecessary endoscopies. Validation of this proposed classification by well designed prospective multicenter studies is required.

CONCLUSIONS

Reflux symptoms are highly prevalent in the general population. Symptoms rather than endoscopy should

be the focus when evaluating patients with GERS. Characterization of patients by symptoms rather than endoscopic findings reflects the practical realities of managing symptoms suggestive of GERD. Such a classification provides a more realistic and practical construct upon which to design management algorithms for primary care providers and should provide clinicians with a practical means of identifying patients with symptoms related to acid, symptoms related to factors other than acid, and those with a combination of both. Studies to assess the clinical and scientific validity of this classification are eagerly awaited.

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