American Journal of Gastroenterology
© 2006 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2006.00630.x

CME

The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus

Nimish Vakil, M.D., F.A.C.G.,[1] Sander V. van Zanten, M.D.,[2] Peter Kahrilas, M.D.,[3] John Dent, M.D.,[4] Roger Jones, M.D.,[5] and the Global Consensus Group

[1]*University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin and Marquette University College of Health Sciences, Milwaukee, Wisconsin;* [2]*Dalhousie University, Halifax, Nova Scotia, Canada;* [3]*Northwestern University, Chicago, Illinois;* [4]*University of Adelaide, Adelaide, Australia; and* [5]*Kings College, London, United Kingdom*

OBJECTIVES: A globally acceptable definition and classification of gastroesophageal reflux disease (GERD) is desirable for research and clinical practice. The aim of this initiative was to develop a consensus definition and classification that would be useful for patients, physicians, and regulatory agencies.

METHODS: A modified Delphi process was employed to reach consensus using repeated iterative voting. A series of statements was developed by a working group of five experts after a systematic review of the literature in three databases (Embase, Cochrane trials register, Medline). Over a period of 2 yr, the statements were developed, modified, and approved through four rounds of voting. The voting group consisted of 44 experts from 18 countries. The final vote was conducted on a 6-point scale and consensus was defined *a priori* as agreement by two-thirds of the participants.

RESULTS: The level of agreement strengthened throughout the process with two-thirds of the participants agreeing with 86%, 88%, 94%, and 100% of statements at each vote, respectively. At the final vote, 94% of the final 51 statements were approved by 90% of the Consensus Group, and 90% of statements were accepted with strong agreement or minor reservation. GERD was defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. The disease was subclassified into esophageal and extraesophageal syndromes. Novel aspects of the new definition include a patient-centered approach that is independent of endoscopic findings, subclassification of the disease into discrete syndromes, and the recognition of laryngitis, cough, asthma, and dental erosions as possible GERD syndromes. It also proposes a new definition for suspected and proven Barrett's esophagus.

CONCLUSIONS: Evidence-based global consensus definitions are possible despite differences in terminology and language, prevalence, and manifestations of the disease in different countries. A global consensus definition for GERD may simplify disease management, allow collaborative research, and make studies more generalizable, assisting patients, physicians, and regulatory agencies.

(Am J Gastroenterol 2006;101:1900–1920)

INTRODUCTION

A number of guidelines and recommendations for the diagnosis and management of gastroesophageal reflux disease (GERD) have been published in different countries, but a universally accepted definition of GERD and its various symptoms and complications is lacking (1–9). Reflux symptoms are common in primary care and GERD is frequently diagnosed based on symptoms alone, but there is no consensus on the distinction of GERD from dyspepsia, so that these terms may lead to confusion in primary care settings. This has led some authorities to combine these entities in primary care management strategies (10). There is also uncertainty about the extraesophageal manifestations of GERD, coupled with an expanding list of putative extraesophageal disorders, resulting in both over- and underdiagnosis of the disease. Finally, the definition of Barrett's esophagus varies in different regions of the world, causing confusion in the assessment of risk and the appropriate use of surveillance.

The aim of this international Consensus Group was to develop a global definition and classification of GERD, using rigorous methodology, that could be used clinically by primary care physicians and that embraces the needs of

To access a continuing medical education exam for this article, please visit www.acg.gi.org/journalcme.

physicians, patients, researchers, and regulatory bodies from different parts of the world.

METHODS

A modified Delphi process was used to develop the consensus definition of GERD (11–13). The Delphi process is a method for developing consensus that has been used for complex problems in medicine and industry. A novel aspect of this endeavor was the combination of the principles of evidence-based medicine, supported by systematic literature reviews, with the Delphi process. A key element of the Delphi process is the use of anonymous voting, which allows a change of views from a previously held position without embarrassment, together with controlled feedback regulated by a nonvoting chairman that prevents the process from being hijacked by a vocal minority. Systematic literature reviews were chosen to support the evidence base as this orientates the consensus process away from clinical opinion to methodologically sound evidence. Multiple iterations of the statements that make up the definition and classification were created until consensus was reached.

The principal steps in the process were: (1) Selection of the Consensus Group and development of draft statements by a Working Group; (2) Systematic literature reviews to identify the evidence to support each statement; (3) Grading of the evidence; (4) Voting discussion and repeated anonymous voting on a series of iterations of the statements until a consensus was reached. Each of these steps is described in more detail below.

Consensus Group Selection

Members of the Consensus Group were selected using several criteria:

1. Demonstrated knowledge/expertise in GERD by publication/research or participation in national or regional GERD consensus guidelines or an interest in guideline development and dissemination.
2. Geographical considerations: individuals who met the criteria under (1) were then invited to provide broad representation of different regions of the world (North America, South America, Asia, Europe, Australia) that have differences in prevalence and manifestation.
3. Diversity of views and expertise related to GERD (including experts in Barrett's esophagus, surgeons, and primary care physicians).

The Consensus Group was led by a nonvoting chairman (NV). The Working Group, who are the primary authors of this article, developed the initial statements and prepared and reviewed the evidence to support the statements that were presented to the Consensus Group. The Consensus Group, which included the Working Group, consisted of 44 experts from 18 countries: Argentina, Australia, Belgium, Brazil, Canada, China, Denmark, France, Germany, Hong Kong, Italy, Japan, Mexico, Netherlands, Peru, Sweden, United Kingdom, and the United States.

Systematic Searches

Systematic literature reviews, with defined inclusion and exclusion criteria, were conducted to identify and grade the available evidence to support each statement. Literature searches were conducted of English language publications in Medline, Embase, and the Cochrane trials register, in human subjects from 1980 onwards. Searches of meeting abstracts (American College of Gastroenterology, American Gastroenterological Association, British Society of Gastroenterology, United European Gastroenterology Week) and review articles were limited to the preceding 2 yr. A number of search strings were used that are too numerous to list in the article. A complete list of the search strings may be obtained by communicating with the lead author of this article. Due to the large number of citations retrieved on each of the topics, the primary reviewer reviewed each of the abstracts and selected articles and meeting abstracts for further review. The review was qualitative and the primary reviewer reached an assessment on the grade assigned to the statement that was then reviewed in the Working Group. Quantitative meta-analyses were not performed. The references cited in this article are a fraction of the articles reviewed in each area and were selected to amplify the statements and the discussion in the Working Group.

Grades of Evidence

Assignment of the grade of evidence for each statement, where applicable, employed the GRADE system, which takes into account the type of evidence while increasing or decreasing the grade depending on the quality of the study and data (14). The final grade provides a practical indication of the likely impact of further research on confidence in the estimate of effect. The grading of evidence is as follows:

- High: Further research is unlikely to change our confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is likely to have an important impact on our confidence in the estimate of effect and is very likely to change the estimate.
- Very low: Any estimate of effect is uncertain.

An initial assessment of grade was made by the primary reviewer of the topic from within the Working Group. The assigned grade was then discussed within the Working Group and a final determination of grade was made. Assignment of grade was not voted upon in the broader Consensus Group. A grade of not applicable was chosen for definitions or statements that cannot be influenced by research. For

example a cluster of symptoms that is defined as a syndrome is an arbitrary designation and cannot be altered by research.

Voting

The entire process lasted 2 yr and the Consensus Group voted on four iterations of the statements. Between each of the four votes, statements were revised by the Working Group based on feedback from the Consensus Group and additional literature reviews. All votes were anonymous.

1. A first vote (baseline) was conducted for the entire Consensus Group electronically (by e-mail), without explanation or justification of the statements, and the results were collated (Vote 1). Feedback on the statements was solicited.
2. A meeting of the entire Consensus Group was held to discuss suggested modifications based on feedback from the first vote and to review and discuss the evidence to support specific statements. Subsequently, a second vote was held, using electronic keypads to ensure anonymity (Vote 2).
3. Focus subgroups were created within the Consensus Group to address controversies in Barrett's esophagus and extraesophageal syndromes. Statements were again revised, this time with input from the focus subgroups. A third electronic vote was conducted by e-mail (Vote 3).
4. A final Consensus Group meeting was held and the complete results of the previous votes were reviewed, followed by an open discussion of all statements, including focused presentations on those statements where there was still lack of consensus. This culminated in the fourth and final vote, using keypads (Vote 4).

Regulatory agencies were invited to the initiative and the European Medicines Agency was represented by a nonvoting observer at the final Consensus Group meeting.

For the first two votes, a simple 2-point scale (agree/disagree) was used in order to rapidly identify areas where consensus/lack of consensus existed. For the third and fourth votes, a 6-point Likert scale was used: 1, agree strongly (A+); 2, agree with minor reservation (A); 3, agree with major reservation (A−); 4, disagree with major reservation (D−); 5, disagree with minor reservation (D); 6, disagree strongly (D+). Agreement with a statement (A+, A, or A−) by two-thirds (*i.e.*, ≥67%) of the group was defined *a priori* as consensus. The level of agreement in the final vote is given for each statement, expressed as the percentage vote at each point on the Likert scale.

Funding Sources

The process was funded by an unrestricted grant from AstraZeneca Research and Development. The European Medicines Agency was responsible for the costs of their observer.

Endorsement by the World Organization of Gastroenterology

The final document was endorsed by the World Organization of Gastroenterology (WGO-OMGE) as "an important development in a critical area of gastroenterology worldwide." "Montreal" is in the title because the results of the study were first presented at the World Congress of Gastroenterology in Montreal.

RESULTS AND DISCUSSION

Overview of the Voting on Statements

A total of 57 statements were presented for the baseline Vote 1 and, following discussion of the supporting evidence, for Vote 2. The statements were subsequently revised and consolidated, providing 53 statements for Vote 3. Further discussion and modification at the final Consensus Group meeting resulted in 51 statements for the final Vote 4.

The level of consensus increased with each round of voting, with a high level of consensus in the fourth and final vote (Fig. 1). At each of the four votes, there was consensus (agreement by ≥67% of the group) on 86%, 88%, 94%, and finally 100% of statements, respectively. Over 90% of the group agreed with 94% (48) of the 51 final statements. Moreover the strength of agreement was very high by the final vote, as illustrated by the average percentage vote across the final 51 statements at each level of the 6-point Likert scale (Table 1). Following the final vote it became apparent that one statement had become redundant as it was already addressed in a preceding statement. Consequently, statements and accompanying commentary are given for 50 rather than 51 statements.

Voting on the Process and Sponsor Influence

Anonymous votes were also obtained on the Delphi process and the influence of the sponsor on the outcome. Ninety percent of participants agreed that the voting process was fair and that they had a chance to input adequately. Ninety-two

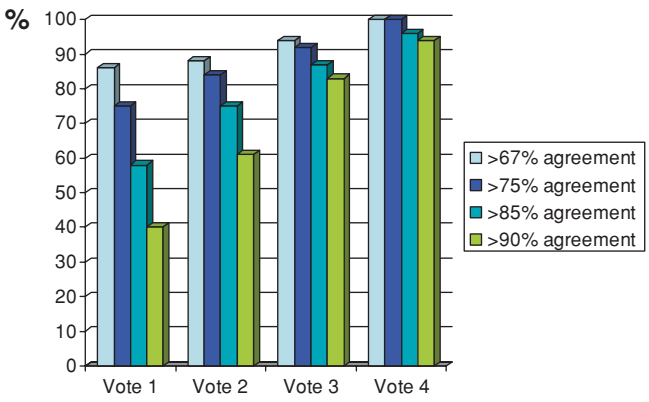

Figure 1. Percentage of statements at each level of agreement at each vote.

Table 1. The Average Percentage for the Final Vote, Across the Final 51 Statements, at Each Level of the 6-Point Scale

A+	Agree strongly	67.2%
A	Agree with minor reservation	23.4%
A−	Agree with major reservation	6.7%
D−	Disagree with major reservation	1.5%
D	Disagree with minor reservation	0.9%
D+	Disagree strongly	0.3%

percent of the participants agreed that the sponsor had not, in any way, influenced their voting

THE GLOBAL DEFINITION OF GERD.

1. **GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications**

Level of agreement: A+, 81%; A, 14%; A−, 5%; D−, 0%; D, 0%; D+, 0% (*Grade: Not applicable*)

We used the general definition of a disease to arrive at a definition of GERD, *i.e.*, a disease is defined as a morbid entity characterized usually by at least two of these criteria: (1) recognized etiologic agent(s); (2) identifiable group of signs and symptoms; (3) consistent anatomic alterations (15). We considered a number of descriptive terms before choosing "troublesome" because it satisfactorily describes the negative aspects of the symptoms from a patient's standpoint, allows itself to be translated into a number of languages, and recognizes the variability in how symptoms impact individual patients. The group recognized that the characteristic symptoms of GERD are retrosternal burning (often labeled heartburn) and regurgitation, and the most common manifestation of esophageal injury is reflux esophagitis (16–18).

The language of the definition is designed to allow asymptomatic patients with complications such as Barrett's esophagus to be included in the case-definition of GERD, and be independent of technology used to achieve a diagnosis. For example, patients may be diagnosed based on typical symptoms alone or on the basis of investigations that demonstrate reflux of stomach contents (*e.g.*, pH testing, impedence monitoring) or the injurious effects of the reflux (endoscopy, histology, electron microscopy), in the presence of typical or atypical symptoms or complications (19, 20). The new definition also recognizes that the refluxate causing symptoms may be weakly acidic or gaseous and these patients also meet the case-definition of GERD.

Classification of the manifestations of GERD: There is a conceptual change in the classification of GERD-related disease manifestations in that it is presented as a set of syndromes (Fig. 2). A syndrome has been defined as the aggregate of symptoms and signs associated with any morbid process, and constituting the picture of the disease (15). In preliminary voting there was over 90% agreement with this definition of a syndrome and with the syndrome-based approach to the definition of GERD, reflecting the clinical reality that patients with GERD may present in a number of ways.

We divided the manifestations of GERD into esophageal and extraesophageal syndromes, with extraesophageal syndromes divided into established and proposed associations (Fig. 2). 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. The rationale for this terminology was that clinicians may need to define and classify patients based on differing amounts of information. In primary care, for example, many patients do not undergo endoscopy to make a diagnosis of GERD and many patients who do, have no abnormalities at endoscopy. The proposed consensus definition therefore allows symptoms to define the disease but permits further characterization if mucosal injury is found. The concept of nonerosive reflux disease is preserved in the typical reflux syndrome without esophageal injury, while reflux esophagitis falls under the category of esophageal syndromes with esophageal injury. The terms ENRD (endoscopy negative reflux disease) and NERD (nonerosive reflux disease), while recognized in the statements, were not used in the classification scheme as they are based entirely on a diagnostic test (endoscopy) that may not be utilized in many patients and which is itself likely to evolve with new instruments and techniques, *e.g.*, magnification endoscopy.

Within the category of esophageal symptomatic syndromes, the reflux chest pain syndrome is listed separately recognizing a group of patients who may present with chest pain without the associated symptoms of the typical reflux syndrome or with pain overshadowing typical reflux symptoms. Within the syndromes with esophageal injury are the well-recognized aspects of mucosal injury including reflux esophagitis, stricture, Barrett's esophagus, and adenocarcinoma. The term reflux esophagitis was preferred over erosive esophagitis because it is increasingly recognized that the demonstration of esophageal erosions may vary with the technology being used. For example, patients with no erosions at endoscopy may prove to have erosions using specialized techniques such as magnification endoscopy. Similarly, patients with no abnormalities at endoscopy may have abnormalities on histological examination at electron microscopy such as dilated intercellular channels (21). A major advantage of this new terminology and classification is that it is likely to endure despite changes in technology that improve our ability to detect esophageal injury.

2. **GERD is common and its prevalence varies in different parts of the world**

Level of agreement: A+, 84%; A, 14%; A−, 2%; D−, 0%; D, 0%; D+, 0% *(Grade: High)*

Population-based studies suggest that GERD is a common condition with a prevalence of 10–20% in Western Europe

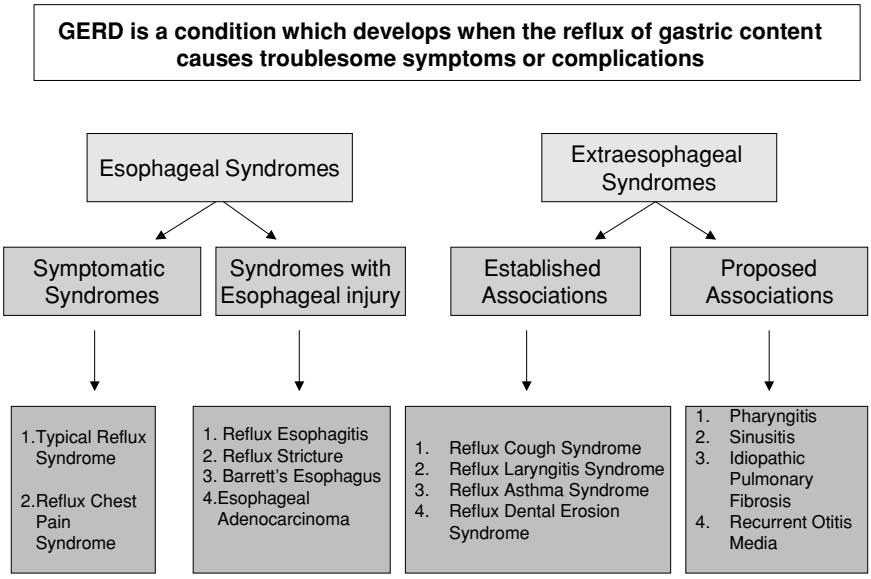

Figure 2. The overall definition of GERD and its constituent syndromes.

and North America (22, 23). The prevalence rates in South America (10%) and Turkey (11.9%) are similar to European countries (24, 25). In Asia, the prevalence has been variably reported but is generally lower. Chen *et al.* reported that the prevalence of heartburn occurring weekly was 6.2% while Wong *et al.* found a lower prevalence of 2.3% (26, 27). A longitudinal study from Singapore suggests that the prevalence of GERD is increasing with an increase in the prevalence of GERD symptoms from 5.5% of the population in 1994 to 10.5% in 1999 (28). Few population-based studies are available from Africa but the available data suggest that in sub-Saharan Africa, GERD and its complications are rare (29).

3. **Symptoms related to gastroesophageal reflux become troublesome when they adversely affect an individual's well-being**

Level of agreement: A+, 70%; A, 30%; A−, 0%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

4. **Reflux symptoms that are not troublesome should not be diagnosed as GERD**

Level of agreement: A+, 56%; A, 28%; A−, 9%; D−, 5%; D, 2%; D+, 0% *(Grade: Not applicable)*

Inherent in the overall definition (Statement 1) is the need to define when symptoms reach a threshold at which they are troublesome to the patient, given that occasional heartburn is common and does not, by itself, constitute a disease. This is addressed by these two statements, in which the word "troublesome" was chosen from a number of other possibilities, such as "bothersome," "troubling," "annoying," etc., following an exercise to determine comprehensibility in several languages and the accuracy of back translation. Quality of life as measured by generic and disease-specific quality of life instruments deteriorates as the severity of GERD symptoms increases (30–32). However, quality of life can be affected by a number of parameters and cannot be readily measured in clinical practice. In contrast, well-being is a patient-centered end point that is easily understood and is therefore used in the definition of GERD rather than quality of life.

An important caveat to the statement on nontroublesome reflux symptoms is that patients may be asymptomatic and may still have underlying complications such as reflux esophagitis or Barrett's esophagus and thereby meet the criteria for the case-definition of GERD. (Statement 1).

5. **In population-based studies, mild symptoms occurring 2 or more days a week, or moderate/severe symptoms occurring more than 1 day a week, are often considered troublesome by patients**

Level of agreement: A+, 44%; A, 46%; A−, 5%; D−, 5%; D, 0%; D+, 0% *(Grade: Moderate)*

6. **In clinical practice, the patient should determine if their reflux symptoms are troublesome**

Level of agreement: A+, 60%; A, 35%; A−, 5%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

The group felt that population-based studies that attempt to define a threshold at which symptoms become troublesome were useful in planning large treatment trials or epidemiologic studies but they were of limited utility in clinical practice. The Consensus Group therefore concluded that in clinical practice the determination of whether symptoms were troublesome should be patient-centered without the use of arbitrary cutoffs for frequency and duration. Data from population-based studies are limited but provide a glimpse of the effects of GERD in a population. In a population-based study in Sweden, symptoms of heartburn or upper abdominal pain that were mild or worse were associated with a clinically meaningful reduction in well-being (33). Data for symptom frequency come from a population-based study of two communities in northern Sweden. (34). Mild symptoms on 2 or

more days a week were associated with a significant reduction in quality of life measured by a disease-specific instrument (QOLRAD). Similar data have been reported from a cohort in the United States (35).

ESOPHAGEAL SYNDROMES: SYMPTOMATIC. These syndromes are defined by the constellation of symptoms and may or may not be characterized by further diagnostic tests.

Typical reflux syndrome: The typical reflux syndrome is defined by the presence of troublesome heartburn and/or regurgitation. Patients may also have other symptoms such as epigastric pain or sleep disturbance.

7. **Heartburn is defined as a burning sensation in the retrosternal area (behind the breastbone)**

Level of agreement: A+, 79%; A, 21%; A−, 0%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

Heartburn is a term that translates poorly into many languages, so that various terms, that are not literal translations of heartburn but are used by patients as well as doctors, are employed in many countries. A definition is needed to provide a clear description of this symptom. Early iterations of this statement also included a substernal element (defined as the central part of the upper abdomen immediately below the breastbone area), but this was removed because of possible confusion over the location of the burning sensation, and the qualifier was added to the retrosternal location in the statement.

8. **Regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx**

Level of agreement: A+, 65%; A, 28%; A−, 7%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

Regurgitation has been variably described in most clinical trials and epidemiological studies on GERD. The definition developed by the Consensus Group is sufficiently rigorous for future epidemiological and clinical research, although this consensus definition was arrived at after considerable debate. Some members initially felt that regurgitation included the perception of gastric content entering the esophagus while others felt that it required the gastric content to enter the mouth or hypopharynx. After much discussion, the consensus statement (above) was agreed upon.

9. **Heartburn and regurgitation are the characteristic symptoms of the typical reflux syndrome**

Level of agreement: A+, 95%; A, 5%; A−, 0%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

Studies in this area are limited by the lack of a gold standard for the diagnosis of GERD. We identified 40 studies reporting the prevalence of heartburn in GERD. Among these, however, we were unable to find a single study that examined unselected individuals with heartburn and correlated the findings with both endoscopy and pH monitoring, or any that calculated the sensitivity, specificity, and predictive values of heartburn for an endoscopic and pH-metry diagnosis of GERD. The much-cited study by Klauser *et al.*, in which a sensitivity of 78% and specificity of 60% for heartburn were reported, was conducted on a highly selected population referred for pH monitoring (16). In patients who previously had antireflux surgery, Eubanks and colleagues found that heartburn was the only symptom to have a significant correlation with acid exposure, and had a positive predictive value of 43% and a negative predictive value of 82%, with overall accuracy of 78% (36). There has been some discussion of the value of "dominant heartburn" in the diagnosis of GERD. A study from the United Kingdom showed that patients with "dominant heartburn" have a little over 50% chance of having GERD as defined by 24-h esophageal pH studies (37).Various studies of patients with GERD, including those entered into large proton pump inhibitor (PPI) trials, indicate that the prevalence of heartburn and regurgitation 75–98% and 48–91%, respectively (38–41).

Our literature search relating to the etiology and management of regurgitation revealed variability in assumptions on the relationship of heartburn and regurgitation. Of the 300 references examined, 163 related to adult GERD and demonstrated that, even in the most recent studies, heartburn and regurgitation are generally described together or as "heartburn or regurgitation" (42). This suggests that there is a belief that each symptom is equally and independently typical of GERD. This view is also held for Asian populations (43). The evidence for this belief comes mostly from the description of symptoms in patients with GERD entered into therapeutic trials of acid suppression, although even in trials the two characteristic GERD symptoms tend to be lumped together, or use heartburn scores as the principal end point (44). As discussed above, much of the variability in this area is attributable to lack of consistency in the definition of heartburn and regurgitation. It is hoped that this will be improved by adoption of the definitions in preceding statements.

10. **Gastroesophageal reflux is the most common cause of heartburn**

Level of agreement: A+, 88%; A, 12%; A−, 0%; D−, 0%; D, 0%; D+, 0% *(Grade: High)*

Heartburn has many causes, but of the 34 studies identified, none were able to accurately describe the frequencies of acid and nonacid causes of heartburn in unselected patients. Indirect evidence for acid causing most heartburn comes from the multitude of therapeutic trials of acid suppression in GERD. The relationship between acid suppression and relief of heartburn is indirectly demonstrated by trials of acid suppression. A recent Cochrane meta-analysis of short-term treatment trials in GERD showed that the relative risk (RR) of relief from heartburn increased with greater degrees of acid suppression: prokinetic agents (RR 0.86, CI 0.73–1.01), H_2-receptor antagonists (RR 0.77, CI 0.60–0.99), PPIs (RR 0.37, CI 0.32–0.44) (45). As suppression of acid is very effective in alleviating heartburn, this provides indirect evidence for the association between acid reflux and heartburn.

11. **Heartburn can have a number of nonreflux related causes. The prevalence of these is unknown**

Level of agreement: A+, 65%; A, 31%; A−, 2%; D−, 0%; D, 2%; D+, 0% *(Grade: Moderate)*

Most studies examining the relevance of nonacidic or weakly acidic causes of heartburn have been conducted in patients with persistent/refractory symptoms, in selected secondary or tertiary care populations, or in postoperative patients (46). The importance of heartburn in this setting has often been emphasized and discussed but infrequently quantified (47, 48). A careful study of poorly responsive heartburn patients, using pH monitoring and Bilitec monitoring during PPI therapy, found that duodenogastric reflux played a role in the genesis of symptoms (49). Using impedance and pH recordings, it has been found that gas reflux, with and without drops in pH, particularly in patients with reflux-attributed laryngeal lesions, coincided with symptoms (50). What remains unclear is the extent to which nonacid or weakly acid reflux plays a role in the genesis of GERD symptoms in untreated patients, although it is clear from these and other studies that acid reflux is far more common than nonacid reflux, but that this pattern changes when PPI treatment is initiated (51).

12. **The typical reflux syndrome can be diagnosed on the basis of the characteristic symptoms, without diagnostic testing**

Level of agreement: A+, 79%; A, 16%; A−, 5%; D−, 0%; D, 0%; D+, 0% *(Grade: Moderate)*

13. **Nonerosive reflux disease is defined by the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy**

Level of agreement: A+, 81%; A, 12%; A−, 7%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

Because the typical reflux syndrome is defined symptomatically, it can be diagnosed on the basis of a clinical history, without the need for diagnostic testing. This is supported by a recent systematic evaluation of approaches to symptom evaluation in GERD (52). Furthermore, patients with characteristic reflux symptoms but no esophageal injury at endoscopy meet the criteria of the typical reflux syndrome. The absence of visible erosions is reported in over 50% of patients presenting with reflux symptoms in primary care, but if their symptoms are troublesome, they have the typical reflux syndrome (53–57). These statements have a strong message for primary care physicians, faced with the need to make a clinical diagnosis and to minimize expensive investigation, and are supported by the meta-analysis of treatment trials referred to earlier (45).

14. **Epigastric pain can be the major symptom of GERD**

Level of agreement: A+, 49%; A, 28%; A−, 14%; D−, 2%; D, 7%; D+, 0% *(Grade: Moderate)*

Perfusion of dilute acid into the distal esophagus has been shown to cause epigastric pain, but there are few data on the prevalence of epigastric pain in reflux disease (58). Some authors have suggested that most patients with pain or discomfort centered in the upper abdomen (dyspepsia) who respond to acid suppression have acid reflux when they undergo pH testing (59). In two large randomized controlled trials of acid inhibition in nonerosive reflux disease, 69% of patients had epigastric pain in addition to symptoms of heartburn (60). All patients had undergone endoscopy to rule out the presence of significant mucosal disease of the esophagus so that this is a selected population. Acid-suppressive therapy resolved heartburn and epigastric pain in these patients and there was a strong correlation between the resolution of heartburn and the resolution of epigastric pain. As most endoscopic tests in patients with epigastric pain do not reveal any significant abnormalities, studies such as these raise the question of whether the typical reflux syndrome is the principal cause of epigastric pain in nonulcer dyspepsia as well. A recent study has identified a subset of heartburn-negative functional dyspepsia patients, with moderate to severe epigastric pain, who also have pathological esophageal acid exposure (61).

15. **GERD is frequently associated with sleep disturbance**

Level of agreement: A+, 44%; A, 37%; A−, 15%; D−, 2%; D, 0%; D+, 2% *(Grade: Moderate, as fully published data are as yet limited)*

This statement is supported by a large general population survey that found that heartburn occurred during the sleep period in 25% of 15,314 respondents and also by surveys of patients with reflux disease that have reported a prevalence of sleep disturbance ascribed to heartburn and/or regurgitation ranging from 23% to 81% (62–66). Similar data come from clinical trials that examine sleep disturbance prior to the start of therapy for reflux disease (67–69). The methods used to assess sleep disturbance have varied from polysomnography to fully validated questionnaires and single questions of uncertain validity. The increase of interest in this area means that several important studies are not yet fully reported.

16. **Night-time heartburn and sleep disturbance reported by patients with GERD are substantially improved by PPI therapy or antireflux surgery**

Level of agreement: A+, 51%; A, 36%; A−, 11%; D−, 2%; D, 0%; D+, 0% *(Grade: Moderate, as fully published data are as yet limited)*

Therapeutic studies of reflux disease provide the most extensive data to support a causal link between reflux disease and sleep disturbance. One large scale placebo-controlled trial of acid suppression in reflux disease patients provides the most rigorous support of the statement (70). Other less well-controlled or smaller studies are also supportive (66–69, 71).

17. **Physical exercise may induce troublesome symptoms of GERD in patients who have no/minimal symptoms at other times (exercise-induced gastroesophageal reflux)**

Level of agreement: A+, 65%; A, 30%; A−, 5%; D− 0%; D, 0%; D+, 0% *(Grade: Low)*

Symptoms of GERD can develop with physical exercise. Exercise-induced gastroesophageal reflux is a well-recognized condition, that has been studied in the laboratory and in controlled environments. However, little community-based or epidemiological data are presently available. Stationary cycling, running, and weight training can produce reflux in healthy volunteers (72). Experiments using graded exercise in athletes have revealed reductions in the duration, amplitude, and frequency of esophageal contractions, accompanied by increases in the number of gastroesophageal reflux episodes and the duration of acid exposure during exercise, particularly at the most intense levels of exercise (73, 74). These physiological changes appear to be dependent both on the nature of the exercise and its intensity. Similar results have been obtained in untrained subjects. More recently, these data have been replicated for other activities, although research in trained cyclists has suggested that the physical agitation and movement of the body may be more important than the exercise *per se* in producing these symptoms (75, 76). There appears to be no correlation between gastroesophageal reflux and exercise-induced bronchoconstriction or asthma (77). In a small study of 14 subjects with heartburn studied during exercise, only a minority of symptomatic episodes were associated with reflux episodes. Exercise worsened reflux by pH-metry, and PPI therapy decreased reflux episodes as measured by pH studies. However, symptoms improved only in patients with a symptom index >50% (78). Exercise-induced gastroesophageal reflux is not characterized by any specific signs or complications. Furthermore, the important and potentially confusing links with exercise-induced chest pain and ischemic heart disease need to be borne in mind.

Reflux chest pain syndrome:

18. **Chest pain indistinguishable from ischemic cardiac pain can be caused by GERD**

Level of agreement: A+, 79%; A, 14%; A−, 7%; D−, 0%; D, 0%; D+, 0% *(Grade: High)*

19. **Gastroesophageal reflux can cause episodes of chest pain that resemble ischemic cardiac pain, without accompanying heartburn or regurgitation**

Level of agreement: A+, 74%; A, 19%; A− 5%; D−, 2%; D, 0%; D+, 0% *(Grade: Moderate)*

We found 178 articles on "noncardiac chest pain" and GERD. Few were based in the community or in primary care, and these were generally of cross-sectional design. In a study using the general practice research database (GPRD), a cohort of 13,740 patients with new onset chest pain in 1996 was identified and compared with an age- and sex-matched sample of 20,000 nonchest pain patients (79). At 1-yr follow-up the odds ratio (OR) for a diagnosis of GERD was 3.0, for dyspepsia 2.7, and for peptic ulcer disease 3.0. The ORs for ischemic heart disease and heart failure were 14.9 and 4.7, respectively. Richards and colleagues in Glasgow showed that in a large community sample of chest pain sufferers, with an overall prevalence of chest pain of approximately 15%, noncardiac pain was more common than angina in men and women in the more affluent social strata, but that the prevalence of cardiac pain exceeded that of noncardiac pain in both men and women in lower socioeconomic groups (80). A number of studies have reported population prevalences of noncardiac chest pain of up to 25% (81–83).

A more recent Australian population-based study found a prevalence of noncardiac chest pain of 32% in men and 39% in women (84). The prevalence of diagnosed ischemic heart disease was 7%, while heartburn and acid regurgitation were both significantly and independently associated. A study in Hong Kong, using similar methodology to Richards *et al.*, found a population prevalence of chest pain of 20.6%, and that GERD was present in 51% of subjects with noncardiac chest pain, which was also associated with higher levels of depression and anxiety (80, 85).

In their Swedish primary care follow-up study, Nilsson and colleagues examined 38,075 general practitioner consultations, of which 577 (1.5%) were for chest pain (86). Ischemic heart disease was diagnosed in 8% of these and excluded in 83%, of which the majority were thought to have a musculoskeletal cause. An esophageal cause was suspected in 10% although the nonischemic heart disease patients were not investigated by endoscopy or pH-metry. More research into the relationship between chest pain and GERD is necessary to clarify some of these issues.

20. **Esophageal motor disorders can cause pain that resembles ischemic cardiac pain by a mechanism separate from gastroesophageal reflux**

Level of agreement: A+, 77%; A, 23%; A−, 0%; D−, 0%; D, 0%; D+, 0% *(Grade: Moderate)*

21. **Gastroesophageal reflux is more frequently a cause of chest pain than esophageal motor disorders**

Level of agreement: A+, 77%; A, 21%; A−, 2%; D−, 0%; D, 0%; D+, 0% *(Grade: Moderate)*

The importance of gastroesophageal reflux, compared with esophageal motor disorders, in causing noncardiac chest pain is demonstrated both by analysis of treatment trials of acid suppression in noncardiac chest pain, summarized in a recent meta-analysis, and by the relative infrequency with which motor abnormalities are found in noncardiac chest pain, except when associated with significant dysphagia (87–89). In a study of 140 patients undergoing esophageal manometry for noncardiac chest pain, manometry was normal in 70% of patients and the most frequent abnormality was a hypotensive lower esophageal sphincter (61% of abnormal studies). Spastic motility disorders, such as nutcracker esophagus (10%), hypertensive lower esophageal sphincter (10%), and diffuse esophageal spasm (2%), were much less common (89).

ESOPHAGEAL SYNDROMES: SYNDROMES WITH ESOPHAGEAL INJURY.

22. **Esophageal complications of gastroesophageal reflux disease are reflux esophagitis, hemorrhage, stricture, Barrett's esophagus, and adenocarcinoma**

Level of agreement: A+, 42%; A, 26%; A−, 16%; D−, 9%; D, 7%; D+, 0% *(Grade: High)*

In clinical practice, endoscopic esophagitis is seen in less than 50% of patients with typical GERD symptoms (90–93). Esophageal erosions, *i.e.*, reflux esophagitis, therefore represent the most common consequence of esophageal injury rather than the principal manifestation of GERD. Reflux esophagitis is the most common manifestation of esophageal injury. The advantage of the term reflux esophagitis is that it can be easily documented during endoscopy and provides an objective criterion for diagnosis. Healing of reflux esophagitis can also be used as a reliable end point for success of therapy and correlates well with improvement of symptoms. Indeed, the fact that acid inhibition heals reflux esophagitis supports the notion that it is a manifestation of GERD.

Esophagitis may also be found at histopathology. Microscopic changes of the esophageal mucosa can be present in patients who do not have endoscopically visible esophagitis but the reliability of histology in making a diagnosis of GERD has been questioned (94). Histological abnormalities include an increase in polymorphonuclear and mononuclear white cells, basal cell hyperplasia, and elongation of the papilla (95). Electron microscopic abnormalities, such as dilated intercellular spaces, have been described in nonerosive reflux disease (96).

Other less common complications of GERD are hemorrhage, stricture, Barrett's esophagus, and adenocarcinoma of the distal esophagus (97, 98). Bleeding due to GERD is rare and is mainly seen in patients who have esophageal ulcers (99). The other manifestations of esophageal injury listed above are addressed in more detail in subsequent statements.

Reflux esophagitis:

23. **Reflux esophagitis is defined endoscopically by visible breaks of the distal esophageal mucosa**

Level of agreement: A+, 93%; A, 7%; A−, 0%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

Reflux esophagitis is diagnosed by endoscopy when visible breaks are seen in the esophageal mucosa at or immediately above the GE junction. Various classification systems have been published to grade the severity of endoscopic esophagitis. Over the last 10 yr the Los Angeles classification has gained general acceptance (100–102). There is strong evidence that visible breaks in the mucosa are the most reliable endoscopic sign of esophagitis (100–104). Other findings such as erythema at the GE junction or an irregular Z-line have proven not to be reliable findings for a diagnosis of reflux esophagitis (103, 104).

24. **Mucosal breaks may be intermittently present in patients with the reflux esophagitis syndrome**

Level of agreement: A+, 65%; A, 28%; A−, 5%; D−, 2%; D, 0%; D+, 0% *(Grade: Low)*

25. **Over a 20-yr period, the severity of reflux esophagitis does not increase in most patients**

Level of agreement: A+, 12%; A, 44%; A−, 37%; D−, 5%; D, 2%; D+, 0% *(Grade: Low)*

Data on the natural course of GERD are sparse. Few studies have specifically investigated whether severity of symptoms or severity of complications, especially reflux esophagitis, change over time. Large studies of the natural history of GERD are unlikely to be conducted, as the majority of patients will be treated for their symptoms. The available limited evidence suggests that the severity of GERD symptoms, both on and off treatment, does not change over time in most patients (91, 105–110). There is also evidence that in most patients GERD is a chronic condition and that symptoms will persist (105–110). Consequently many of these patients will require long-term treatment either continuously or intermittently. In this statement "a 20-yr period" was added because there are no published data beyond this time frame. It is likely that slow progression will occur in a proportion of patients. The data showing that older individuals have more severe esophagitis, and that the prevalence of complications such as Barrett's esophagus and cancer increases with age, support this notion (111). A very limited number of studies have evaluated whether endoscopic findings, such as presence or absence of reflux esophagitis or grade of esophagitis, are stable over time. A few studies suggest that mucosal breaks may be intermittently present in patients who were previously diagnosed with reflux esophagitis (105–107, 109). Similarly, reflux esophagitis will be seen in a proportion of patients in whom an earlier endoscopy did not reveal endoscopic abnormalities, suggesting that progression may take place at a slow rate in a subset of patients (105–107, 109). One problem that is frequently encountered in practice is that many patients are already receiving, or have recently received, treatment when they come for endoscopy. This will make it difficult to make definitive statements about whether the patient ever had reflux esophagitis.

26. **Although heartburn frequency and intensity correlate with the severity of mucosal injury, neither will accurately predict the severity of mucosal injury in the individual patient**

Level of agreement: A+, 65%; A, 21%; A−, 9%; D−, 5%; D, 0%; D+, 0% *(Grade: Moderate)*

Factors that predict the presence of esophagitis are the frequency and duration of reflux episodes, occurrence of day and night time reflux episodes, and the presence of a hiatus hernia (112–116). Although the frequency and intensity of symptoms have been shown to have a moderate correlation with severity of endoscopic findings in several studies, generally symptoms will not accurately predict what the endoscopic findings will be in an individual patient (93, 112–116). Furthermore, for elderly patients there are data to suggest that despite evidence of more severe esophagitis, the

intensity of heartburn symptoms was less when compared to younger patients (111). By relying on heartburn severity one may therefore underestimate the severity of esophagitis in elderly patients (111). Similarly, there is also some evidence that patients with Barrett's esophagus may report less frequent or less severe symptoms (117).

Reflux stricture:

27. **A reflux stricture is defined as a persistent luminal narrowing of the esophagus caused by GERD**

Level of agreement: A+, 93%; A, 7%; A−, 0%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

28. **The characteristic symptom of a stricture is persistent troublesome dysphagia**

Level of agreement: A+, 96%; A, 2%; A−, 2%; D− 0%; D, 0%; D+, 0% *(Grade: High)*

29. **Dysphagia is a perceived impairment of the passage of food from the mouth into the stomach**

Level of agreement: A+, 84%; A, 11%; A−, 5%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

A reflux stricture can develop as a result of severe reflux disease, when inflammation results in narrowing of the esophageal lumen so that passage of food is impaired. This is seen in <5% of GERD patients (91). Usually patients who have a reflux stricture will complain of persistent and troublesome dysphagia. Often such patients will require endoscopic dilatation in addition to acid suppressive therapy to obtain improvement in dysphagia symptoms.

The term dysphagia should be limited to the sensation of impeded passage of solid food or liquids through the esophagus, while oropharyngeal dysphagia is difficulty with the movement of solids or liquids from the mouth into the esophagus, which is unrelated to GERD. Odynophagia is defined as painful swallowing and is a common symptom in infectious esophagitis (*e.g.*, candida, herpes).

An important component of the new GERD definition is that symptoms are troublesome. Troublesome dysphagia is more related to solids than liquids. Nontroublesome dysphagia is common in GERD. In a combined analysis of 11,495 patients with erosive esophagitis, 37% reported dysphagia when a symptom checklist was used. Dysphagia resolved in most patients (83%) following treatment with a PPI (118).

30. **Troublesome dysphagia is present when patients need to alter eating patterns or report food impaction**

Level of agreement: A+, 75%; A, 19%; A−, 2%; D−, 2%; D, 2%; D+, 0% *(Grade: Not applicable)*

31. **Dysphagia is troublesome in a small proportion of patients with GERD**

Level of agreement: A+, 70%; A, 28%; A−, 2%; D−, 0%; D, 0%; D+, 0% *(Grade: Low)*

32. **Persistent, progressive, or troublesome dysphagia is a warning symptom for stricture or cancer of the esophagus and warrants investigation**

Level of agreement: A+, 88%; A, 10%; A−, 0%; D−, 0%; D, 2%; D+, 0% *(Grade: High)*

Troublesome dysphagia is present when patients need to alter their eating patterns or have symptoms of solid food getting impacted. Dysphagia is troublesome only in a minority of GERD patients. There is agreement that troublesome and worsening dysphagia, especially for solids, is an alarm symptom. It warrants investigation, as it could be indicative of more serious pathology, such as a peptic stricture or cancer of the esophagus. Recent reviews have confirmed that having dysphagia increases the risk (OR 3–4) of having an upper GI malignancy (119, 120).

Barrett's esophagus:

33. **The term Barrett's esophagus is variably interpreted at the present time and lacks the clarity needed for clinical and scientific communication about columnar metaplasia of the esophageal mucosa**

Level of agreement: A+, 63%; A, 19%; A−, 11%; D−, 7%; D, 0%; D+, 0% *(Grade: Not applicable)*

There is a universal agreement that the core component of all of the varying definitions of Barrett's esophagus is the partial replacement, from the gastroesophageal junction proximally, of esophageal squamous epithelium with metaplastic columnar epithelium. The term "Barrett's esophagus" is currently confusing and ambiguous because the spectrum of what is currently referred to as "Barrett's esophagus" ranges from some clinicians making this diagnosis solely on the basis of endoscopic appearances of any extent, to the requirement that intestinal-type esophageal columnar metaplasia be proven histologically before this diagnosis is made (121, 122). A recent study in clinical practice in Munich showed that the consistency of endoscopic and histological findings between an index endoscopy and one performed 2 yr later was poor, with similar results obtained in only one-third of patients (123). In patients in whom the endoscopy initially suggested Barrett's esophagus but the biopsy was not confirmatory of intestinal metaplasia, 42% of patients did not have Barrett's esophagus at endoscopy or on histology at a subsequent examination. Thus, there appears to be a variability in the endoscopic diagnosis of Barrett's esophagus as well. Some of these results may be explained by biopsy sampling error or the demonstration of gastric metaplasia at biopsy. These differing usages were acknowledged as a problem by the Consensus Group. At a recent workshop, 72% of the 18 physicians reviewing the data on Barrett's esophagus agreed that esophageal intestinal metaplasia documented by histology was a prerequisite for the diagnosis of Barrett's esophagus, while 16% had major reservations with this requirement for the definition and 12% rejected this concept (124). A subsequent study examining the conformity between practicing U.S. gastroenterologists and the workshop group found further disparities in opinion. Only 72% of practicing U.S. gastroenterologists agreed that intestinal metaplasia was a prerequisite for the diagnosis of Barrett's esophagus (125). These data suggest the notion that intestinal metaplasia is a

prerequisite for the diagnosis of Barrett's esophagus is not uniformly accepted even in the United States where this concept originated.

34. **Neither the frequency nor the severity of heartburn is useful for prediction of the presence, type, or extent of esophageal columnar metaplasia**

Level of agreement: A+, 84%; A, 12%; A−, 2%; D−, 0%; D, 2%; D+, 0% *(Grade: Moderate)*

The qualifier "useful" in this statement was taken to mean the ability to recognize individual patients with esophageal columnar metaplasia on the basis of heartburn severity and frequency alone. It was readily agreed that these criteria are not discriminatory (126–128). It has also been shown that 5.6–25% of older people free of troublesome heartburn have evidence of esophageal columnar metaplasia (19, 129). For patients with reflux disease, detailed analysis of factors such as age, gender, and duration and pattern of reflux symptoms can identify individuals at an increased risk of having esophageal columnar metaplasia (127, 128, 130).

35. **Endoscopically suspected esophageal metaplasia (ESEM) describes endoscopic findings consistent with Barrett's esophagus that await histological evaluation**

Level of agreement: A+, 72%; A, 24%; A−, 2%; D−, 0%; D, 2%; D+, 0% *(Grade: Not applicable)*

It was agreed that there should be a terminology that differentiates a purely endoscopic diagnosis of esophageal columnar metaplasia from one that is confirmed histologically. Recent studies have shown that there may be a marked disparity between endoscopic and biopsy findings. In one recent study, a group of patients with suspected Barrett's esophagus at endoscopy and no evidence of intestinal metaplasia at biopsy underwent repeat endoscopy 2 yr later (123). At the second examination, 42% of patients had no endoscopic or histological evidence of Barrett's esophagus and 46% continued to have apparent Barrett's esophagus at endoscopy without biopsy confirmation of intestinal metaplasia. These data suggest that the endoscopic diagnosis needs confirmation with histology and that a term that acknowledges the possibility that the endoscopic appearance may not be diagnostic was chosen. The option "endoscopically suspected Barrett's esophagus" was considered, but the more neutral, descriptive terminology given in the statement was preferred, in the belief that this would be of less concern to patients and their insurers and would prevent patients from being mistakenly labeled as having Barrett's esophagus before histological confirmation was obtained (131) (Fig. 3).

36. **Multiple, closely spaced biopsies are necessary to characterize ESEM**

Level of agreement: A+, 79%; A, 17%; A−, 0%; D−, 2%; D, 2%; D+, 0% *(Grade: High)*

Effective management of the risk for esophageal adenocarcinoma requires sensitive detection of intestinal-type metaplasia (see Statement 41) and high-grade dysplasia (122, 132). These histological abnormalities, particularly high-grade dysplasia, frequently occupy a very small proportion of the surface area of columnar metaplasia (133, 134). Though research into novel endoscopic techniques suggests that it may, in the future, be possible to recognize areas of metaplastic mucosa likely to contain changes of particular clinical relevance and to target biopsies to these areas, this is currently not an established option in routine clinical practice (135, 136). Thus, current biopsy practice must sample all areas of metaplastic mucosa as thoroughly as possible (122, 132). The best researched biopsy protocol is four-quadrant biopsies every 1 cm for circumferential metaplastic segments, which is substantially more sensitive than sampling at 2-cm intervals (133, 137). This approach has been variably modified to include biopsies at the top of tongue-like metaplastic extensions. These onerous and usually expensive protocols are generally not accepted as best practice (122, 132). Even with the use of such protocols, there is still evidence of significant sampling inaccuracies, since concordance for the finding of presence or absence of intestinal-type metaplasia between first, second, and even third endoscopies is relatively poor, especially for segments shorter than 3 cm (123, 138, 139). It has been found that intestinal-type metaplasia is most prevalent at the most proximal extent of metaplasia (140).

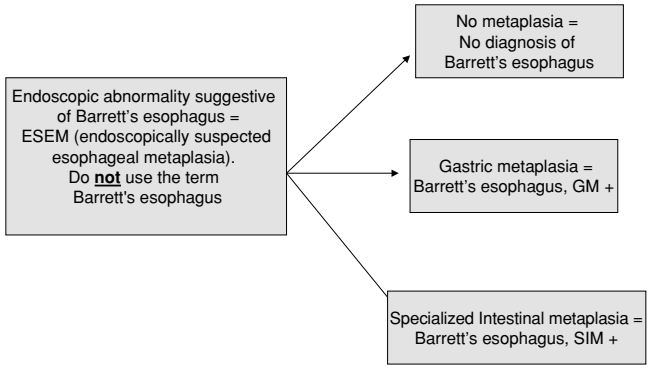

Figure 3. Consensus terminology for Barrett's esophagus.

37. **The description of ESEM should include a standardized measure of endoscopic extent**

Level of agreement: A+, 88%; A,12%; A−, 0%; D−, 0%; D, 0%; D+, 0% *(Grade: Not applicable)*

Reliable unambiguous measures of extent are desirable for clinical communication and research into esophageal columnar metaplasia. The risk for adenocarcinoma is significantly influenced by the extent of metaplasia. If all esophageal columnar metaplasia is considered, around three quarters of cases appear to have metaplasia less than 3 cm in extent and the cancer risk is less in these patients than in those with more extensive metaplasia (98, 141, 142). There is an evidence of a continuum of increasing risk for cancer with increasing extent of metaplasia beyond 3 cm (98, 143).

"Standardized" is an important qualifying word in the statement. There has been insufficient research into the best approaches to endoscopic measurement of extent.

Accordingly, differing approaches have been used in published studies, with resultant difficulties in making comparisons among studies or with pooling their data. The lack of a validated, standard approach to measurement of extent means that this clinically relevant variable is often poorly described and in terms that are open to interpretation. Recently, however, an international working group has developed standard criteria that may aid further research (144).

38. **When biopsies of ESEM show columnar epithelium it should be called Barrett's esophagus and the presence or absence of intestinal-type metaplasia specified**

Level of agreement: A+, 49%; A, 28%; A−, 9%; D−, 5%; D, 2%; D+, 7% *(Grade: Not applicable)*

This statement is the final product of the most controversial topic of the workshop. In the early phase of discussion it was decided that the eponymous term "Barrett" should be retained in any definition because it would be futile and counterproductive to try to remove such an embedded word from general use. Pragmatism aside, opinion was divided as to whether Barrett's original scientific contribution warranted continued use of his name as a label, but this was not put to formal discussion and voting. With retention of the word "Barrett" decided, there was eventual consensus that all types of histologically proven esophageal columnar metaplasia should be included under this umbrella word, with the important added descriptors of either "intestinal-type metaplasia positive" or "negative" (see statement above). One major reason for the statement and the voting on it was the far from perfect sensitivity of even a rigorous biopsy protocol for detection of intestinal-type metaplasia (see Statement 36), let alone the less rigorous biopsy protocols used in routine clinical practice in every part of the world where practice has been surveyed (145–147). This is not just a problem of tissue sampling, since the staining techniques and interpretation of biopsies can influence the sensitivity of detection of intestinal-type metaplasia (148, 149). A literature search failed to reveal any systematic review or meta-analysis of the risk for esophageal adenocarcinoma of definite esophageal columnar metaplasia in which intestinal metaplasia had not been shown to be present, despite careful biopsy sampling (Fig. 3).

Adenocarcinoma:

39. **Adenocarcinoma of the esophagus is a complication of GERD**

Level of agreement: A+, 67%; A, 26%; A−, 7%; D−, 0%; D, 0%; D+, 0% *(Grade: Moderate)*

40. **The risk of adenocarcinoma of the esophagus rises with increasing frequency and duration of heartburn**

Level of agreement: A+, 47%; A, 42%; A−, 7%; D−, 0%; D, 2%; D+, 2% *(Grade: Moderate)*

There is strong epidemiological evidence, especially from case-control studies in Sweden, that esophageal adenocarcinoma is a complication of GERD and that chronic GERD symptoms increase the risk of esophageal adenocarcinoma (97, 98). In the study by Lagergren *et al*. the risk of esophageal adenocarcinoma was increased (OR 7.7) in patients suffering from longstanding reflux symptoms (97). Higher frequency (greater than 3 times per week) and long duration (greater than 10–20 yr) of symptoms further increased the OR to 16.4 and 20. Over the last 25 yr there has been a remarkable change in the epidemiology of esophageal cancer in Western countries. The incidence of esophageal adenocarcinoma has been rising substantially although the absolute lifetime risk of developing adenocarcinoma is <1% (97, 150–152). In addition, until recently, the incidence of esophageal squamous cell carcinoma used to be much higher than esophageal adenocarcinoma. According to recent data from the United States, the incidence of adenocarcinoma of the esophagus now has surpassed the rate of squamous carcinoma (151). The rise in adenocarcinoma incidence is in keeping with the rising GERD prevalence in other parts of the world. For example in Japan, where the disease used to be rare, the prevalence of GERD is increasing, as are Barrett's esophagus and esophageal adenocarcinoma (153, 154).

41. **Long-segment Barrett's esophagus with intestinal-type metaplasia is the most important identified risk factor for esophageal adenocarcinoma**

Level of agreement: A+, 67%; A, 21%; A−, 12%; D−, 0%; D, 0%; D+, 0% *(Grade: High)*

A wealth of consistently supportive data resulted in prompt consensus on this statement (see Statement 37) (97, 132, 155, 156). Wang *et al*. have tabulated the reported experience on adenocarcinoma development from endoscopic surveillance studies (132). A large scale prospective Swedish study of patients with the diagnosis of esophageal adenocarcinoma provides the most definitive data (97). It is unclear what proportion of the esophageal columnar metaplasia-negative cases noted in this study were accounted for either by destruction of esophageal columnar metaplasia by cancer or by misclassification of adenocarcinoma of the gastric cardia as esophageal adenocarcinoma (97).

EXTRAESOPHAGEAL SYNDROMES: ESTABLISHED ASSOCIATIONS. Although a great amount has been published on the extraesophageal GERD syndromes, little of this represents high-level original work. This realization prompted an evolution in the statements regarding the extraesophageal syndromes, as paucity of evidence supporting the initial versions became apparent. Thus, whereas in the initial iterations, the statements strongly suggested causality between reflux and cough, laryngitis, asthma, and dental erosions, the final iterations were much more restrained, emphasizing (1) the existence of an association between these syndromes and GERD, (2) the rarity of extraesophageal syndromes occurring in isolation without a concomitant manifestations of the typical esophageal syndrome, (3) that these syndromes are usually multifactorial with GERD as one of the several potential aggravating cofactors, and (4) that data

substantiating a beneficial effect of reflux treatments on the extraesophageal syndromes are weak.

Reflux cough, reflux laryngitis, and reflux asthma syndromes:

42. **Chronic cough, chronic laryngitis, and asthma are significantly associated with GERD**

Level of agreement: A+, 39%; A, 26%; A−, 28%; D−, 7%; D, 0%; D+, 0% *(Grade: High)*

43. **Chronic cough, chronic laryngitis, and asthma are usually multifactorial disease processes and gastroesophageal reflux can be an aggravating cofactor**

Level of agreement: A+, 63%; A, 23%; A−, 12%; D−, 2%; D, 0%; D+, 0% *(Grade: Cough Low, Laryngitis Low, Asthma High)*

44. **Gastroesophageal reflux is rarely the sole cause of chronic cough, chronic laryngitis, or asthma**

Level of agreement: A+, 65%; A, 23%; A−, 7%; D−, 5%; D, 0%; D+, 0% *(Grade: Cough Low, Laryngitis Very Low, Asthma High)*

Three large population-based surveys have demonstrated an increased risk of numerous ENT and pulmonary symptoms among patients with either esophagitis or reflux symptoms (81, 157, 158). The reported ORs for having laryngeal or pulmonary conditions among GERD patients in these studies range from 1.2 to 3.0, with nocturnal cough having the strongest association.

Support for the premise that chronic cough, chronic laryngitis, or asthma are multifactorial processes with reflux as a potential aggravating factor comes from therapeutic trials in which these entities were improved, but incompletely resolved, by treating reflux disease. In the case of reflux cough syndrome, the only randomized controlled trials of medical therapy found no treatment effect (159–161). Thus, one has to look to observational trials of antireflux surgery (162–164) and these are by nature subject to selection and referral bias. By and large these trials show improvement in cough scores as a result of treatment. With respect to reflux laryngitis syndrome, there are no randomized controlled treatment trials in which chronic laryngitis patients exhibited a complete treatment response. Observational trials of medical or surgical therapy report partial improvement in laryngitis symptomatology and in some cases laryngoscopic appearance (164, 165). Commonly implicated cofactors with laryngitis include heavy voice usage, habitual throat clearing, allergic rhinitis with postnasal drip, infectious laryngitis, and environmental irritants including smoking. Regarding reflux asthma syndrome, Field summarized the medical and surgical data and concluded that there was a significant benefit in improving asthma symptoms and reducing asthma medication usage but no improvement in pulmonary function attributable to GERD therapy (166, 167). Commonly implicated cofactors among asthma patients include allergens, exercise, temperature or climate changes, or emotional conflicts.

Since reflux disease has highly effective treatments, it follows that manifestations of the disease should exhibit high-grade treatment effects. Thus, support for the premise that reflux is the sole cause of chronic cough, chronic laryngitis, or asthma would come from therapeutic trials in which these entities were completely resolved by treating reflux disease. In the case of chronic cough, few, if any, patients within randomized controlled trials exhibited a complete treatment response (159–161). The strongest evidence of a complete treatment effect comes from an uncontrolled observational study of laparoscopic Nissen fundoplication in which 51% of 133 chronic cough patients exhibited a complete symptom response following the procedure (162). In a smaller observational study of 8 carefully studied chronic patients who were refractory to medical therapy, 2 subsequently exhibited a complete cough resolution after antireflux surgery (163). Both of these series enrolled highly selected patients, suggesting that although chronic cough can be entirely attributable to reflux, this is a rare occurrence. With respect to chronic laryngitis, there are no randomized controlled treatment trials for GERD in which patients exhibited a complete treatment response. Observational treatment trials of medical or surgical therapy report partial symptomatic improvement and in some cases laryngoscopic appearance but few, if any, patients experienced a complete laryngitis response (164, 165). With respect to reflux asthma syndrome, Field concluded that there was no objective improvement in pulmonary function attributable to medical therapy of GERD (166). Furthermore, a recent longitudinal epidemiological study of more than 14,000 patients in U.K. general practice found that patients with a new diagnosis of asthma are at significantly increased risk for developing GERD rather than *vice versa* (168). However, two randomized controlled trials of antireflux surgery as treatment for asthma reported subsets of patients in the surgically treated arms with complete asthma resolution; 6 of 16 in the Sontag *et al*. study and 11 of 22 in the Larrain *et al*. study (169, 170). Pulmonary function data are not provided in the Larrain *et al*. study. Thus, only a subset of patients has asthma entirely attributable to reflux, and this subset is probably small.

45. **Potential causal mechanisms of reflux cough, reflux laryngitis, and reflux asthma syndromes include direct (aspiration) or indirect (neurally mediated) effects of gastroesophageal reflux**

Level of agreement: A+, 61%; A, 28%; A−, 7%; D−, 2%; D, 0%; D+, 2% *(Grade: High)*

Experimental evidence in both animals and humans has demonstrated reflex stimulation of bronchospasm and cough as a response to esophageal acidification (171, 172). Animal studies have also demonstrated the development of laryngeal ulceration and profound bronchospasm as a result of the direct application of acid to the larynx or acid instillation into the airway (173, 174). Studies of pulmonary function in asthmatics have demonstrated correlation between lung

resistance and the occurrence of spontaneous gastroesophageal reflux (175).

46. **In the absence of heartburn or regurgitation, unexplained asthma and laryngitis are unlikely to be related to GERD**

Level of agreement: A+, 37%; A, 33%; A−, 14%; D−, 7%; D, 9%; D+, 0% *(Grade: Laryngitis Low, Asthma High)*

This statement implies that individuals with conclusive reflux laryngitis and reflux asthma syndromes usually have esophageal manifestations of reflux as well. Since the only patients in whom these diagnoses can be confidently established are those that convincingly responded to reflux treatment, it is the responders who must be evaluated with respect to whether or not they had frequent heartburn. With respect to reflux laryngitis syndrome, the only randomized controlled trials demonstrating a treatment effect were on patients with clear-cut reflux disease in addition to the laryngitis, whereas the recent trial that excluded patients with frequent heartburn demonstrated no benefit of a PPI over placebo in treating the laryngitis (176–178). With respect to asthma, most asthmatics have objective evidence of reflux disease as well as reflux symptoms (179). A recent randomized controlled study of 770 asthmatics evaluated twice-daily PPI therapy and only the patient group with both nocturnal respiratory and GERD symptoms responded to the PPI better than to placebo in the primary study outcome measure (morning peak expiratory flow) (180). In the two randomized controlled trials of antireflux surgery that showed treatment benefit with respect to asthma, objective evidence of reflux was either an entry criterion for the study or objectively demonstrated in almost all patients (169, 170).

47. **Medical and surgical treatment trials aimed at improving presumed reflux cough, reflux laryngitis, and reflux asthma syndromes by treating GERD are associated with uncertain and inconsistent treatment effect**

Level of agreement: A+, 51%; A, 40%; A−, 7%; D−, 0%; D, 0%; D+, 2% *(Grade: Cough Very Low, Laryngitis Moderate, Asthma High)*

In the case of reflux cough syndrome, two small randomized controlled trials have evaluated the effects of PPI treatment on chronic cough. One of these found no significant improvement in cough between the PPI and placebo groups (12% *vs* 0%) with only 1 of 8 patients randomized to the PPI showing a response (159). However, during subsequent, open-label treatment 5 of the 9 placebo-treated patients, all of whom had markedly abnormal pH studies, responded dramatically. The other randomized controlled PPI trial was compromised by a crossover design that the authors concluded resulted in treatment effect from the first period carrying over to the second. When the analysis was restricted to the group randomized to initial placebo therapy (N = 13), a significant reduction in cough score was demonstrated when they crossed over to PPI (160). Crossover studies are prone to overestimating treatment effect and these studies should be viewed with caution. One randomized controlled trial of H_2-receptor antagonist therapy for chronic cough showed no therapeutic benefit (161). Several uncontrolled trials on H_2-receptor antagonists, with or without prokinetics, have reported improvement in cough in 70–100% of treated patients (176, 177, 181, 182). With respect to treatment of suspected reflux cough syndrome with antireflux surgery, there are no controlled trials. There are, however, consistently positive results from uncontrolled studies suggesting benefit in a subset of chronic cough patients but these studies have the usual limitations in that they overestimate treatment effect (164, 183).

For reflux laryngitis there are four published randomized controlled trials using twice-daily PPI therapy for 8–12 wk encompassing a total of 88 patients (176, 177, 181, 182). One additional study of 88 patients has thus far been published only in abstract form (178). One trial showed a significant difference between the PPI and placebo in resolution of laryngeal symptoms and one other for hoarseness and throat clearing (159, 177). No significant difference in laryngoscopic healing was found between placebo and PPI-treated groups in any of the trials. There are substantial inconsistencies among the trials in laryngoscopic criteria for defining reflux laryngitis, pH-monitoring protocols, and most importantly, inclusion of patients with concomitant heartburn. The trial with the best therapeutic result enrolled patients with-high-grade, unequivocal laryngoscopic findings and markedly abnormal esophageal pH-monitoring studies (161). The large treatment trial finding no PPI benefit enrolled patients with low-grade laryngoscopic findings and excluded patients with frequent heartburn (178).

With respect to reflux asthma syndrome, Field concluded that there was a significant benefit in improving asthma symptoms and reducing asthma medication usage but no objective improvement in pulmonary function attributable to GERD therapy (166, 170, 184–190). A recent large study, using esomeprazole 40 mg twice daily, enrolled a total of 770 patients and subdivided asthmatics into those with only nocturnal respiratory symptoms, only nocturnal GERD symptoms, or both nocturnal respiratory and GERD symptoms. The primary outcome variable was the change in morning peak expiratory flow. Of the three patient groups, only those with both nocturnal respiratory and GERD symptoms responded to esomeprazole better than to placebo with a mean difference in morning peak expiratory flow of 8.7 L/min (180). A difference of 20 L/min is generally considered the threshold for clinical significance. Also of interest is a recent study analyzing a subset of asthmatic patients with cough and reflux (191). This uncontrolled treatment trial demonstrated substantial improvement in cough, pulmonary function, asthma symptoms, and reflux symptoms (when present) after 3 months of PPI therapy (esomeprazole 40 mg once daily). In a complementary analysis of the effects of antireflux surgery on asthma, there were only two controlled trials again showing improvement

in asthma symptoms and medication use but no improvement in pulmonary function (167, 169, 170). Similar to the case with the laryngitis studies, there are substantial inconsistencies among trials in asthma definition and in whether or not patients with well-defined or symptomatically evident GERD were included. Of particular note, the largest placebo-controlled trial of surgical therapy was a three-armed trial involving 90 patients conducted by a single group of investigators (170). This trial, which reported the best therapeutic results in both the medical and surgical domain, excluded patients with "allergic" asthma and required that they had reflux symptoms.

Reflux dental erosion syndrome:

48. **The prevalence of dental erosions, especially on the lingual and palatal tooth surfaces, is increased in patients with GERD**

Level of agreement: A+, 42%; A, 35%; A−, 19%; D−, 2%; D, 0%; D+, 2%*(Grade: High)*

In a prospective consecutive series, 253 patients were divided into two groups based on reflux symptoms: 181 refluxers and 72 controls (192). The percentage with dental erosions was significantly higher among the reflux group (47.5% *vs* 12.5% $p < 0.001$) but there were no differences in other clinical or dental parameters. A similar analysis among intellectually disabled individuals found 19 of 29 individuals (65.5%) with dental erosions to have pH-monitoring criteria for GERD compared to only 9 of 34 without dental erosions (26.5%) ($p = 0.04$) (193). Another study found a positive correlation between esophageal acid exposure measured by pH monitoring and dental erosion score among 30 patients with and without GERD (194).

EXTRAESOPHAGEAL SYNDROMES: PROPOSED ASSOCIATIONS.

49. **It is unclear whether gastroesophageal reflux is a significant causal or exacerbating factor in the pathogenesis of sinusitis, pulmonary fibrosis, pharyngitis, or recurrent otitis media**

Level of agreement: A+, 91%; A, 9%; A−, 0%; D−, 0%; D, 0%; D+, 0% *(Grade: Low, reflecting lack of authoritative mechanistic or therapeutic studies)*

The generally low quality, uncontrolled published studies relevant to this statement have been reviewed recently (195, 196). Epidemiological studies have shown a modestly increased OR for sinusitis in the U.S. military veterans with reflux esophagitis of 1.6 (1.51–1.70) (157). This risk is slightly higher at 2.34 (1.72–3.19) for children with GERD (197). Adequate evidence of causal linkage is lacking. U.S. military veterans with reflux esophagitis have a slightly increased risk for idiopathic pulmonary fibrosis, with an OR of 1.36 (1.25–1.48) (157). There is no persuasive evidence of causal linkage. There are no authoritative, confirmed data that indicate GERD is a clinically significant contributor to pharyngitis or otitis media.

50. **It is unclear whether gastroesophageal reflux plays a role in triggering apneic episodes in patients with obstructive sleep apnea**

Level of agreement: A+, 74%; A, 21%; A−, 5%; D−, 0%; D, 0%; D+, 0% *(Grade: Low, because of lack of direct mechanistic study data)*

An increased prevalence of GERD has been found consistently in obstructive sleep apnea patients, but uncertainty remains whether reflux episodes are true precipitants of apneic episodes (198–204). The argument that lack of correlation of severity of reflux-induced symptoms with severity of obstructive sleep apnea is an evidence against precipitation of apneic episodes by reflux episodes is unconvincing (205). More definitive mechanistic data are required.

CONCLUSIONS

In conclusion, a new definition and classification of GERD has been developed by an International Consensus Group. It provides a basis for universally accepted terminology that bridges cultures and countries and may simplify disease management, allow collaborative research, and make studies more generalizable, assisting patients, physicians, and regulatory agencies. Coupling evidence-based medicine with modern consensus development techniques allows a broad consensus among different regions of the world. For practicing physicians, this definition and classification clarify the criteria necessary for a diagnosis of GERD, simplify the classification of suspected and proven Barrett's esophagus, and define the state of our incomplete knowledge in extraesophageal disorders. For patients, the consensus statement provides clarity on a diagnosis that is based on a patient-centered definition of troublesome symptoms and may help to prevent patients from being inappropriately labeled as having Barrett's esophagus. Clarification of the role of GERD in patients with cough and hoarseness may also help the management of patients with these difficult conditions. Finally, regulators may benefit from a uniform terminology and classification to use with clinical trial data submissions.

ACKNOWLEDGMENTS

Other members of the Consensus Group: Lars Agreus (Stockholm, Sweden), David Armstrong (Hamilton, Canada), Stephen Attwood (Manchester, UK), Jean-Francois Bergman (Paris, France), Marc-Andre Bigard (Vandoeuvre-les-Nancy, France), Patricia Blount (Seattle, WA), Peter Bytzer (Glostrup, Denmark), Tsutomu Chiba (Kyoto, Japan), Gianfranco Delle Fave (Rome, Italy), Hashem El-Serag (Houston, TX), Daiming Fan (Xi'an, China), Ronnie Fass (Tucson, AZ), Nigel Flook (Edmonton, Canada), Jean-Paul Galmiche (Nantes, France), Michio Hongo (Sendai, Japan), Francisco

Huerta Iga (Coahuila, Mexico), Janusz Jankowski (Leicester, UK), David Johnson (Norfolk, VR), Folke Johnsson (Lund, Sweden), Peter Katelaris (Concord, Australia), Yoshi Kinoshita (Izumo, Japan), Elly Klinkenberg-Knol (Amsterdam, Netherlands), Joachim Labenz (Siegen, Germany), Harley Liker (Beverly Hills, CA), Peter Malfertheiner (Magdeburg, Germany), Hiroto Miwa (Tokyo, Japan), Paul Moayyedi (Hamilton, Canada), Fabio Pace (Milan, Italy), Joachim Prado (Sao Paulo, Brazil), Joel Richter (Philadelphia, PA), Graciela Salis (Buenos Aires, Argentina), Lin San-Ren (Beijing, China), Prateek Sharma (Kansas City, MO), Vincenzo Stanghellini (Bologna, Italy), Jan Tack (Leuven, Belgium), Nicholas Talley (Rochester, MN), Benjamin Wong (Hong Kong, China), Yuan Yaozong (Shanghai, China), Carlos Zapata (Lima, Peru).

The Barrett's esophagus subgroup comprised Stephen Attwood, Patricia Blount, Peter Malfertheiner, and Nicholas Talley.

The extraesophageal reflux syndromes subgroup comprised Peter Bytzer, Hashem El-Serag, Fabio Pace, and Joel Richter.

Reprint requests and correspondence: Nimish Vakil M.D., F.A.C.G., ASMC, 945 North 12th Street, Room 4040, Milwaukee, WI 53233.

Received December 10, 2005; accepted February 7, 2006.

REFERENCES

1. Jian R, Chassany O, Douet MC, et al. French-Belgian consensus conference on adult gastro-oesophageal reflux disease 'diagnosis and treatment': Report of a meeting held in Paris, France, 21–22 January 1999. Eur J Gastroenterol Hepatol 2000;12:129–37.
2. Koop H, Schepp W, Mueller-Lissner S, et al. Consensus conference of the DGVS on gastro-esophageal reflux. Z Gastroenterol 2005;43:163–93.
3. Hongo M. GERD guideline workshop report 2002. Ther Res 2003;24:830–5.
4. DeVault KR, Castell DO. American College of Gastroenterology. Updated guidelines for the diagnosis and treatment of gastro-esophageal reflux disease. Am J Gastroenterol 2005;100:190–200.
5. National Institute for Clinical Excellence. Management of dyspepsia in adults in primary care. Available at: http://www.nice.org Accessed 7 October 2005.
6. Moraes-Filho JPP, Cecconello I, Gama-Rodrigues J, et al. Brazilian consensus on gastro-esophageal reflux disease: Proposals for assessment, classification, and management. Am J Gastroenterol 2002;97:241–8.
7. Katelaris P, Holloway R, Talley N, et al. Gastro-oesophageal reflux disease in adults: Guidelines for clinicians. J Gastroenterol Hepatol 2002;17:825–33.
8. Fock K, Talley N, Hunt R, et al. Report of the Asia-Pacific consensus on the management of gastro-esophageal reflux disease. J Gastroenterol Hepatol 2004;19:357–67.
9. Armstrong D, Marshall JK, Chiba N, et al. Canadian association of gastroenterology GERD consensus group. Canadian consensus conference on the management of gastro-esophageal reflux disease in adults—update 2004. Can J Gastroenterol 2005;19:15–35.
10. Veldhuyzen van Zanten SJO, Bradette M, Chiba N, et al. Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: An update of the Canadian dyspepsia working group (CanDys) clinical management tool. Can J Gastroenterol 2005;19:285–303.
11. Linstone H, Turoff M. The Delphi method: Techniques and applications. URL: http://www.is.njit.edu/pubs/delphibook/.
12. Dalkey N. An experimental study of group opinion: The Delphi method. Futures 1969;September:408–26.
13. Lomaz J. Words without action? The production, dissemination and impact of consensus recommendations. Annu Rev Public Health 1991;12:41–65.
14. The GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490–4.
15. Stedman's online medical dictionary. Available at: http://www.stedmans.com. Accessed 7 October 2005.
16. Klauser AG, Schindlbeck NE, Muller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. Lancet 1990;335:205–8.
17. Berstad A, Hatlebakk JG. The predictive value of symptoms in gastro-oesophageal reflux disease. Scand J Gastroenterol Suppl 1995;211:1–4.
18. Cicala M, Emerenziani S, Caviglia R, et al. Intra-oesophageal distribution and perception of acid reflux in patients with non-erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2003;18:605–13.
19. Rex DK, Cummings OW, Shaw M, et al. Screening for Barrett's esophagus in colonoscopy patients with and without heartburn. Gastroenterology 2003;125:1670–7.
20. Venables TL, Newland RD, Patel AC, et al. Omeprazole 10 milligrams once daily, omeprazole 20 milligrams once daily, or ranitidine 150 milligrams twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. Scand J Gastroenterol 1997;32:965–73.
21. Caviglia R, Ribolsi M, Maggiano N, et al. Dilated intercellular spaces of esophageal epithelium in nonerosive reflux disease patients with physiological esophageal acid exposure. Am J Gastroenterol 2005;100:543–8.
22. Stanghellini V. Relationship between upper gastrointestinal symptoms and lifestyle, psychosocial factors and comorbidity in the general population: Results from the domestic/international gastroenterology surveillance study (DIGEST). Scand J Gastroenterol Suppl 1999;231:29–37.
23. Dent J, El-Serag HB, Wallander MA, et al. Epidemiology of gastro-oesophageal reflux disease: A systematic review. Gut 2005;54:710–7.
24. Prado J, Moraes-Filho P. Gastro-esophageal reflux disease: Prevalence and management in Brazil. Best Pract Res Clin Gastroenterol 2004;18:23–6.
25. Bor S, Mandiracioglu A, Kitapcioglu G, et al. Gastro-esophageal reflux disease in a low-income region in Turkey. Am J Gastroenterol 2005;100:759–65.
26. Chen M, Xiong L, Chen H, et al. Prevalence, risk factors and impact of gatroesophageal reflux disease symptoms: A population based study in South China. Scand J Gastroenterol 2005;40:750–67.
27. Wong WM, Lai KC, Lam KF, et al. Prevalence, clinical spectrum and health care utilization of gastro-esophageal reflux disease in a Chinese population: A population-based study. Aliment Pharmacol Ther 2003;18:595–604.
28. Lim SL, Goh WT, Lee JM, et al. Community medicine GI studygroup. Changing prevalence of gastro-esophageal reflux with changing time: Longitudinal study in an

Asian population. J Gastroenterol Hepatol 2005;20:995–1001.
29. Segal I. The gastro-esophageal reflux disease complex in sub-Saharan Africa. Eur J Cancer Prev 2001;10:209–12.
30. Revicki DA, Wood M, Maton PN, et al. The impact of gastro-esophageal disease on health-related quality of life. Am J Med 1998;104:252–8.
31. Revicki DA, Wood M, Wiklund I, et al. Reliability and validity of the gastrointestinal symptom rating scale in patients with gastro-esophageal reflux disease. Qual Life Res 1998;1:75–83.
32. Talley NJ, Fullerton S, Junghard O, et al. Quality of life in patients with endoscopy—negative heartburn: Reliability and sensitivity of disease-specific instruments. Am J Gastroenterol 2001;96:1998–2004.
33. Wiklund I, Carlsson J, Vakil N. Gastro-esophageal reflux symptoms and well-being in a random sample of the general population of a Swedish community. Am J Gastroenterol 2006;101:18–28.
34. Aro P, Ronkainen J, Storskrubb T, et al. Quality of life in a general adult population with gastro-esophageal reflux symptoms and/or esophagitis: A report from the Kalixanda study. Gastroenterology 2003;124:A168.
35. Shaw MJ, Adlis S, Beebe T, et al. When does heartburn become a disease? Gastroenterology 1998;114: G1166.
36. Eubanks TR, Omelanczuk P, Richards C, et al. Outcomes of laparoscopic anti-reflux procedures. Am J Surg 2000;179:391–5.
37. Moayyedi P, Axon ATR. The usefulness of the likelihood ratio in the diagnosis of dyspepsia and gastro-esophageal reflux disease. Am J Gastroenterol 1999;94:3122–5.
38. Lin M, Gerson LB, Lascar R, et al. Features of gastro-esophageal reflux disease in women. Am J Gastroenterol 2004;99:1442–7.
39. Vakil NB, Lauritsen K, Junghard O, et al. Esomeprazole provides more effective maintenance therapy following healing of erosive esophagitis in patients with dysphagia at baseline compared with lansoprazole. Gastroenterology 2003;124(4 suppl 1):A-542-3.
40. Jones RH, Hungin APS, Phillips J, et al. Gastro-oesophageal reflux disease in primary care in Europe: Clinical presentation and endoscopic findings. Eur J Gen Pract 1995;1:149–54.
41. Wu JC, Sung JJ, Ng EK, et al. Prevalence and distribution of *Helicobacter pylori* in gastro-esophageal reflux disease: A study from the East. Am J Gastroenterol 1999;4:1790–4.
42. Nilsson M, Johnsen R, Ye W, et al. Prevalence of gastro-oesophageal reflux symptoms and the influence of age and sex. Scand J Gastroenterol 2004;39:1040–5.
43. Kusano M. Diagnosis and investigation of gastro-oesophageal reflux disease in Japanese patients. Aliment Pharmacol Ther 2004;29(suppl 8):14–8.
44. Bochenek WJ, Mack ME, Fraga PD, et al. Pantoprazole provides rapid and sustained relief in patients treated for erosive oesophasitis. Aliment Pharmacol Ther 2004;20:1105–14.
45. Van Pinxteren B, Numan ME, Bonis PA, et al. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev 2004;(4):CD002095.
46. Marshall RE, Anggiansah A, Owen WA, et al. Investigation of oesophageal reflux symptoms after gastric surgery with combined pH and bilirubin monitoring. Br J Surg 1999;86:271–5.
47. Lin KM, Ueda RK, Hinder RA, et al. Etiology and importance of alkaline oesophageal reflux. Am J Surg 1991;162:553–7.
48. Vaezi MF. 'Refractory GERD': Acid, nonacid or not GERD? Am J Gastroenterol 2004;99:989–90.
49. Tack J, Koek G, Demedts I, et al. Gastro-esophageal reflux disease poorly responsive to single-dose proton pump inhibitors in patients without Barrett's oesophagus: Acid reflux, bile reflux or both? Am J Gastroenterol 2004;99:981–8.
50. Kawamura O, Aslam M, Rittmann T, et al. Physican and pH properties of gastroesophago-pharyngeal refluxate: A 24-hour simultaneous ambulatory impedance and pH monitoring study. Am J Gastroenterol 2004;99:1000–10.
51. Sifrim D, Holloway R, Silny J, et al. Acid, nonacid and gas reflux in patients with gastro-esophageal reflux disease during ambulatory 24-hour pH-impedance recordings. Gastroenterology 2001;120:1588–98.
52. Dent J, Armstrong D, Delaney B, et al. Symptom evaluation in reflux disease: Workshop background, processes, terminology, recommendations, and discussion outputs. Gut 2004;53(suppl 4):iv1–24.
53. Johansson KE, Ask P, Boeryd B, et al. Oesophagitis, signs of reflux, and gastric acid secretion in patients with symptoms of gastro-oesophageal reflux disease. Scand J Gastroenterol 1986;21:837–47.
54. Johnsson F, Joelsson B, Gudmundsson K, et al. Symptoms and endoscopic findings in the diagnosis of gastro-esophageal reflux disease. Scand J Gastroenterol 1987;22:714–8.
55. Joelsson B, Johnsson F. Heartburn—the acid test. Gut 1989;30:1523–5.
56. Robinson M, Earnest D, Rodriguez-Stanley S, et al. Heartburn requiring frequent antacid use may indicate significant illness. Arch Intern Med 1998;158:2373–6.
57. Tefera L, Fein M, Ritter MP, et al. Can the combination of symptoms and endoscopy confirm the presence of gastro-esophageal reflux disease? Am Surg 1997;63:933–6.
58. Earlam RJ. Further experience with epigastric pain reproduction test in duodenal ulceration. BMJ 1972;2:683–5.
59. Farup P, Hovde O, Torp R, et al. Patients with functional dyspepsia responding to omeprazole have a characteristic gastro-esophageal reflux pattern. Scand J Gastroenterol 1999;34:575–9.
60. Vakil N, Katz P, Traxler B, et al. Resolution of epigastric pain accompanies resolution of hearturn in endoscopy-negative GERD. Gastroenterology 2003;124:A-542.
61. Tack J, Caenepeel P, Arts J, et al. Prevalence of acid reflux in functional dyspepsia and its association with symptom profile. Gut 2005;54:1370–6.
62. Fass R, Quan SF, O'Connor GT, et al. Predictors of heartburn during sleep in a large prospective cohort study. Chest 2005;127:1658–66.
63. Farup C, Kleinman L, Sheldon S, et al. The impact of nocturnal symptoms associated with gastro-esophageal reflux disease on health-related quality of life. Arch Intern Med 2001;161:45–52.
64. Shaker R, Castell DO, Schoenfeld PS, et al. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: The results of a Gallup survey conducted on behalf of the American Gastroenterological Association. Am J Gastroenterol 2003;98:1487–93.
65. Elewaut A, Mainguet P, Imschoot J. The impact of severity of pyrosis and regurgitation on quality of sleep (QOS) in patients with esophagitis. Gastroenterology 2004;A-310:M1324.

66. Chand N, Johnson DA, Tabangin M, et al. Sleep dysfunction in patients with gastro-esophageal reflux disease: Prevalence and response to GERD therapy, a pilot study. Aliment Pharmacol Ther 2004;20:969–74.
67. Cohen JA, Arain A, Harris PA, et al. Surgical trial investigating nocturnal gastro-esophageal reflux and sleep (STINGERS). Surg Endosc 2003;17:394–400.
68. Nilsson G, Wenner J, Larsson S, et al. Randomized clinical trial of laparoscopic versus open fundoplication for gastro-esophageal reflux. Br J Surg 2004;91:552–9.
69. Leodolter A, Kulig M, Nocon M, et al. Esomeprazole therapy improves sleep disorders in patients with gastro-esophageal reflux disease (GERD): A report from the ProGerd study. Gastroenterology 2004;A-226: S1585.
70. Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: A randomized, placebo-controlled trial. Am J Gastroenterol 2005;100:1914–22.
71. Pratha V, Wan GJ, Soffer E, et al. Pantoprazole positively impacts nighttime heartburn symptoms and quality of sleep in patients with gastro-esophageal reflux disease. Am J Gastroenterol 2003;(suppl 9):S234:A708.
72. Clark CS, Kraus BB, Sinclair J, et al. Gastro-esophageal reflux induced by exercise in health volunteers. JAMA 1989;261:3599–601.
73. Soffer EE, Merchant RK, Duethman G, et al. Effect of graded exercise on esophageal motility and gastro-esophageal reflux in trained athletes. Dig Dis Sci 1993;38:220–4.
74. Soffer EE, Wilson J, Duethman G, et al. Effect of graded exercise on esophageal motility and gastro-esophageal reflux in nontrained subjects. Dig Dis Sci 1994;39:193–8.
75. Yazaki E, Shawdon A, Beasley I, et al. The effect of different types of exercise on gastro-esophageal reflux. Aust J Sci Med Sport 1996;28:93–6.
76. Van Nieuwenhoven MA, Brouns F, Brummer RJ. The effect of physical exercise on parameters of gastrointestinal function. Neurogastroenterol Motil 1999;11:431–9.
77. Weiner P, Konson N, Sternberg A, et al. Is gastro-esophageal reflux a factor in exercise-induced asthma? Respir Med 1998;92:1071–5.
78. Peters HP, DeKort AF, van Krevelen H, et al. The effect of omeprazole on gastro-esophageal reflux and symptoms during strenuous exercise. Aliment Pharmacol Ther 1999;13:1015–22.
79. Garcia-Rodriguez LA, Wallander M, Johansson S, et al. Natural history of chest pain in GERD. Gut 2005;54(suppl VII):A75, OP-G-325.
80. Richards H, McConnachie A, Morrison C, et al. Social and gender variation in the prevalence, presentation and general practitioner provisional diagnosis of chest pain. J Epidemiol Community Health 2000;54:714–8.
81. Locke GR 3rd, Talley NJ, Fett SL, et al. Prevalence and clinical spectrum of gastro-esophageal reflux: A population-based study in Olmsted county, Minnesota. Gastroenterology 1997;112:1448–56.
82. Brattberg G, Parker MG, Thorslund M. A longitudinal study of pain: Reported pain from middle age to old age. Clin J Pain 1997;13:144–9.
83. Lampe FC, Whincup PH, Wannamethee SG, et al. Chest pain on questionnaire and prediction of major ischaemic heart disease events in men. Eur Heart J 1998;19:63–73.
84. Eslick GD, Jones M, Talley NJ. Non-cardiac chest pain: Prevalence, risk-factors, impact and consulting—a population-based study. Aliment Pharmacol Ther 2003;17:1115–24.
85. Wong WM, Lam KF, Cheng C, et al. Population based study of non cardiac chest pain in southern China: Prevalence, psychosocial factors and health care utilization. World J Gastroenterol 2004;10:707–12.
86. Nilsson S, Scheike M, Engblom D, et al. Chest pain and ischaemic heart disease in primary care. Br J Gen Pract 2003;53:378–82.
87. Cremonini F, Wise J, Moayyedi P, et al. Diagnostic and therapeutic use of proton pump inhibitors in non-cardiac chest pain: A meta-analysis. Am J Gastroenterol 2005;100:1226–32.
88. Ciriza de los Rios C, Garcia Menendez L, Diez Hernandez A, et al. Role of stationary esophageal manometry in clinical practice. Manometric results in patients with gastro-esophageal reflux, dysphagia or non-cardiac chest pain. Rev Esp Enferm Dig 2004;96:606–11.
89. Dekel R, Pearson T, Wendel C, et al. Assessment of oesophageal motor function in patients with dysphagia or chest pain—the clinical outcomes research initiative experience. Aliment Pharmacol Ther 2003;18:1083–9.
90. Dent J, Brun J, Fendrick AM, et al. on behalf of the Genval Working Group. An evidence-based appraisal of reflux disease management—the Genval workshop report. Gut 1999;44(suppl 2):S1–16.
91. Sonnenberg A, El-Serag HB. Clinical epidemiology and natural history of gastro-esophageal reflux disease. Yale J Biol Med 1999;72:81–92.
92. El-Serag HB, Sonnenberg A. Associations between different forms of gastro-esophageal reflux disease. Gut 1997;41:594–9.
93. Thomson ABR, Barkun AN, Armstrong D, et al. The prevalence of clinically significant upper gastrointestinal findings in primary care patients with uninvestigated dyspepsia: The Canadian adult dyspepsia empiric treatment—prompt endoscopy (CADET-PE) study. Aliment Pharmacol Ther 2003;17:1481–91.
94. Nandurkar S, Talley NJ, Martin CJ, et al. Esophageal histology does not provide additional useful information over clinical assessment in identifying reflux patients presenting for esophagogastroduodenoscopy. Dig Dis Sci 2000;45:217–24.
95. Zentilin P, Savarino V, Mastracci L, et al. Reassessment of the diagnostic value of histology in patients with GERD, using multiple biopsy sites and an appropriate control group. Am J Gastroenterol 2005;100:2299–306.
96. Solcia E, Villani L, Luinetti O, et al. Altered intercellular glycoconjugates and dilated intercellular spaces of esophageal epithelium in reflux disease. Virchows Arch 2000;436:207–16.
97. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastro-esophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825–31.
98. Avidan B, Sonnenberg A, Schnell TG, et al. Hiatal hernia size, Barrett's length, and severity of acid reflux are all risk factors for esophageal adenocarcinoma. Am J Gastroenterol 2002;97:1930–6.
99. Niguchi D, Sugawa C, Shah SH, et al. Etiology, treatment, and outcome of esophageal ulcers: A 10-year experience in an urban emergency hospital. J Gastrointest Surg 2003;7:836–42.
100. Armstrong D, Bennett JR, Blum AL, et al. The endoscopic assessment of esophagitis: A progress report on observer agreement. Gastroenterology 1996;111:85–92.
101. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: Clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172–80.

102. Pandolfino JE, Vakil NB, Kahrilas PJ. Comparison of inter- and intraobserver consistency for grading of esophagitis by expert and trainee endoscopists. Gastrointest Endosc 2002;56:639–43.
103. Vieth M, Haringsma J, Delarive J, et al. Red streaks in the oesophagus in patients with reflux disease: Is there a histomorphological correlate? Scand J Gastroenterol 2001;36:1123–7.
104. Bytzer P, Havelund T, Hansen JM. Interobserver variation in the endoscopic diagnosis of reflux esophagitis. Scand J Gastroenterol 1993;28:119–25.
105. Isolauri J, Luostarinen M, Isolauri E, et al. Natural course of gastro-esophageal reflux disease: 17–22 year follow-up of 60 patients. Am J Gastroenterol 1997;92:37–41.
106. McDougall NI, Johnston BT, Collins JS, et al. Three- to 4.5-year prospective study of prognostic indicators in gastro-esophageal reflux disease. Scand J Gastroenterol 1998;33:1016–22.
107. Pace F, Bollani S, Molteni P, et al. Natural history of gastro-esophageal reflux disease without oesophagitis (NERD)—a reappraisal 10 years on. Dig Liver Dis 2004;36:111–5.
108. Schindlbeck NE, Klauser AG, Berghammer G, et al. Three year follow up of patients with gastrooesophageal reflux disease. Gut 1992;33:1016–9.
109. Manabe N, Yoshihara M, Sasaki A, et al. Clinical characteristics and natural history of patients with low-grade reflux esophagitis. J Gastroenterol Hepatol 2002;17:949–54.
110. Garrido Serrano A, Guerrereo Igea F, Lepe Jiminez J, et al. Clinical features and endoscopic progression of gastro-esophageal reflux disease. Rev Esp Enferm Dig 2003;95:712–6.
111. Johnson DA, Fennerty MB. Heartburn severity underestimates erosive esophagitis severity in elderly patients with gastro-esophageal reflux disease. Gastroenterology 2004;126:660–4.
112. Rokkas T, Sladen GE. Ambulatory esophageal pH recording in gastro-esophageal reflux: Relevance to the development of esophagitis. Am J Gastroenterol 1988;83:629–32.
113. Saraswat VA, Dhiman RK, Mishra A, et al. Correlation of 24-hr esophageal pH patterns with clinical features and endoscopy in gastro-esophageal reflux disease. Dig Dis Sci 1994;39:199–205.
114. Eisen GM, Sandler RS, Murray S, et al. The relationship between gastro-esophageal reflux disease and its complications with Barrett's esophagus. Am J Gastroenterol 1997;92:27–31.
115. El-Serag HB, Johanson JF. Risk factors for the severity of erosive esophagitis in *Helicobacter pylori*-negative patients with gastro-esophageal reflux disease. Scand J Gastroenterol 2002;37:899–904.
116. Avidan B, Sonnenberg A, Schnell TG, et al. There are no reliable symptoms for erosive oesophagitis and Barrett's esophagus: Endoscopic diagnosis is still essential. Aliment Pharmacol Ther 2002;16:735–42.
117. Brandt MG, Darling GE, Miller L. Symptoms, acid exposure and motility in patients with Barrett's esophagus. Can J Surg 2004;47:47–51.
118. Vakil NB, Traxler B, Levine D. Dysphagia in patients with erosive esophagitis: Prevalence, severity, and response to proton pump inhibitor treatment. Clin Gastroenterol Hepatol 2004;2:665–8.
119. Kapoor N, Bassi A, Sturgess R, et al. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. Gut 2005;54:40–5.
120. Fransen GA, Janssen MJ, Muris JW, et al. Meta-analysis: The diagnostic value of alarm symptoms for upper gastrointestinal malignancy. Aliment Pharmacol Ther 2004;20:1045–52.
121. Spechler SJ, Goyal RK. The columnar-lined esophagus, intestinal metaplasia, and Norman Barrett. Gastroenterology 1996;110:614–21.
122. Sampliner RE, The Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. Am J Gastroenterol 2002;97:1888–95.
123. Meining A, Ott R, Becker I, et al. The Munich Barrett follow-up study: Suspicion of Barrett's esophagus based on either endoscopy or histology only—what is the clinical significance? Gut 2004;53:1402–7.
124. Sharma P, McQuaid K, Dent J, et al. A critical review of the diagnosis and management of Barrett's esophagus: The AGA Chicago workshop. Gastroenterology 2004;127:310–30.
125. Howden C, Metz D, Chey W, et al. Degree of conformity between US Gastroenterologists and experts concerning Barrett's esophagus. Gastroenterology 2005;128:A-148.
126. Winters C, Spurling TJ, Chobanian SJ, et al. Barrett's esophagus. A prevalent, occult complication of gastro-esophageal reflux disease. Gastroenterology 1987;92:118–24.
127. Locke GR, Zinsmeister AR, Talley NJ. Can symptoms predict endoscopic findings in GERD? Gastrointest Endosc 2003;58:661–70.
128. Lieberman DA, Oehlke M, Helfand M, GORGE Consortium. Risk factors for Barrett's esophagus in community-based practice. Am J Gastroenterol 1997;92:1293–7.
129. Gerson LB, Shetler K, Triadafilopoulos G. Prevalence of Barrett's esophagus in asymptomatic individuals. Gastroenterology 2002;123:461–7.
130. Gerson LB, Edson R, Lavori PW, et al. Use of a simple symptom questionnaire to predict Barrett's esophagus in patients with symptoms of gastro-esophageal reflux. Am J Gastroenterol 2001;96:2005–12.
131. Shaheen NJ, Dulai GS, Ascher B, et al. Effect of a new diagnosis of Barrett's esophagus on insurance status. Am J Gastroenterol 2005;100:577–80.
132. Wang KK, Wongkeesong M, Buttar NS. American Gastroenterological Association technical review on the role of the gastroenterologist in the management of esophageal carcinoma. Gastroenterology 2005;128:1471–505.
133. Reid BJ, Weinstein WM, Lewin KJ, et al. Endoscopic biopsy can detect high-grade dysplasia or early adenocarcinoma in Barrett's esophagus without grossly recognizable neoplastic lesions. Gastroenterology 1988;94:81–90.
134. Thompson JJ, Zinsser KR, Etnerline HT. Barrett's metaplasia and adenocarcinoma of the esophagus and gastro-esophageal junction. Hum Pathol 1983;14:42–61.
135. Sharma P, Weston AP, Topalovski M, et al. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's esophagus. Gut 2003;52:24–7.
136. Hamamoto Y, Endo T, Nosho K, et al. Usefulness of narrow-band imaging endoscopy for diagnosis of Barrett's esophagus. J Gastroenterol 2004;39:14–20.
137. Reid BJ, Blount PL, Feng Z, et al. Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. Am J Gastroenterol 2000;95:3089–96.
138. Kim SL, Waring JP, Spechler SJ, et al, The Department of Veterans Affairs Gastro-esophageal Reflux Study Group. Diagnostic inconsistencies in Barrett's esophagus. Gastroenterology 1994;107:945–9.
139. Jones TF, Sharma P, Daaboul B, et al. Yield of intestinal metaplasia in patients with suspected short-segment

Barrett's esophagus (SSBE) on repeat endoscopy. Dig Dis Sci 2002;27:2108–11.
140. Chandrasoma PT, Der R, Dalton P, et al. Distribution and significance of epithelial types in columnar-lined esophagus. Am J Surg Pathol 2001;25:1188–93.
141. Rudolph RE, Vaughan TL, Storer BE, et al. Effect of segment length on risk for neoplastic progression in patients with Barrett esophagus. Ann Intern Med 2000;132:612–20.
142. Csendes A, Smok G, Burdiles P, et al. Prevalence of intestinal metaplasia according to the length of the specialized columnar epithelium lining the distal esophagus in patients with gastro-esophageal reflux. Dis Esophagus 2003;16:24–8.
143. Weston AP, Badr AS, Hassanein RS. Prospective multivariate analysis of clinical, endoscopic, and histological factors predictive of the development of Barrett's multifocal high-grade dysplasia or adenocarcinoma. Am J Gastroenterol 1999;94:3413–9.
144. Armstrong D. Review article: Towards consistency in the endoscopic diagnosis of Barrett's esophagus and columnar metaplasia. Aliment Pharmacol Ther 2004;20(suppl 5):40–7.
145. Stein HJ, Panel of Experts. Esophageal cancer: Screening and surveillance. Results of a consensus conference held at the VIth world congress of the international society for diseases of the esophagus. Dis Esophagus 1996;9(suppl 1):3–19.
146. MacNeil-Covin L, Casson AG, Malatjalian D, et al. A survey of Canadian gastroenterologists about the management of Barrett's esophagus. Can J Gastroenterol 2003;17:313–7.
147. Gorlet I, Bruley des Varannes S, Le Rhun M, et al. Evaluation du diagnostic endoscopique de l'endobrachyoesophage. Gastroenterol Clin Biol 2003;27:700–7.
148. Nandurkar S, Talley NJ, Martin CJ, et al. Short segment Barrett's esophagus: Prevalence, diagnosis and associations. Gut 1997;40:710–5.
149. Alikhan M, Rex D, Dhan A, et al. Variable pathologic interpretation of columnar lined esophagus by general pathologists in community practice. Gastrointest Endosc 1999;50:23–6.
150. Blot WJ, Devesa SS, Kneller RW, et al. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991;265:1287–9.
151. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. Cancer 1998;83:2049–53.
152. El-Serag HB, Mason AC, Petersen N, et al. Epidemiological differences between adenocarcinoma of the esophagus and adenocarcinoma of the gastric cardia in the USA. Gut 2002;50:368–72.
153. Fujimoto K. Review article: Prevalence and epidemiology of gastro-esophageal reflux disease in Japan. Aliment Pharmacol Ther 2004;20(suppl 8):5–8.
154. Hongo M. Review article: Barrett's esophagus and carcinoma in Japan. Aliment Pharmacol Ther 2004;20(suppl 8):50–4.
155. Jankowski JA, Provenzale D, Moayyedi P. Esophageal adenocarcinoma arising from Barrett's metaplasia has regional variations in the west. Gastroenterology 2002;122:588–95.
156. Solaymani-Dodaran M, Logan RFA, West J, et al. Risk of oesophageal cancer in Barrett's esophagus and gastro-esophageal reflux disease. Gut 2004;53:1070–4.
157. El-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. Gastroenterology 1997;113:755–60.
158. Gislason T, Janson C, Vermeire P, et al. Respiratory symptoms and nocturnal gastro-esophageal reflux: A population based study of young adults in three European countries. Chest 2002;121:158–63.
159. Ours TM, Kavuru MS, Schilz RJ, et al. A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. Am J Gastroenterol 1999;94:3131–8.
160. Kiljander TO, Salomaa ERM, Hietanen EK, et al. Chronic cough and gastro-esophageal reflux: A double-blind placebo-controlled study with omeprazole. Eur Respir J 2000;16:633–8.
161. Ing AJ, Ngu MC, Breslin ABX. A randomised double blind placebo controlled crossover study of ranitidine in patients with chronic persistent cough (CPC) associated with gastro-esophageal reflux (GOR). Am Rev Respir Dis 1992;145:A11.
162. Allen CJ, Anvari M. Gastro-esophageal reflux related cough and its response to laparoscopic fundoplication. Thorax 1998;53:963–8.
163. Irwin RS, Zawacki JK, Wilson MM, et al. Chronic cough due to gastro-esophageal reflux disease: Failure to resolve despite total/near-total elimination of esophageal acid. Chest 2002;121:1132–40.
164. So JB, Zeitels SM, Rattner DW. Outcomes of atypical symptoms attributed to gastro-esophageal reflux treated by laparoscopic fundoplication. Surgery 1998;124:28–32.
165. Kamel PL, Hanson D, Kahrilas PJ. Prospective trial of omeprazole in the treatment of posterior laryngitis. Am J Med 1994;96:321–6.
166. Field SK, Sutherland LR. Does medical antireflux therapy improve asthma in asthmatics with gastro-esophageal reflux? A critical review of the literature. Chest 1998;114:275–83.
167. Field SK. The effects of antireflux surgery on asthmatics with gastro-esophageal reflux. Chest 1999;116:766–74.
168. Ruigómez A, Rodríguez G, Wallander M, et al. Gastro-esophageal reflux disease and asthma. A longitudinal study in UK general practice. Chest 2005;128:85–93.
169. Sontag SJ, O'Connell S, Khandelwal S, et al. Asthmatics with gastro-esophageal reflux: Long term results of a randomized trial of medical and surgical antireflux therapies. Am J Gastroenterol 2003;98:987–99.
170. Larrain A, Carrasco E, Galleguillos F, et al. Medical and surgical treatment of nonallergic asthma associated with gastro-esophageal reflux. Chest 1991;99:1330–5.
171. Field SK, Evans JA, Price LM. The effects of acid perfusion of the esophagus on ventilation and respiratory sensation. Am J Respir Crit Care Med 1998;157:1058–62.
172. Ing AJ, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastro-esophageal reflux. Am J Respir Crit Care Med 1994;149:160–7.
173. Adhami T, Goldblum JR, Richter JE, et al. The role of gastric and duodenal agents in laryngeal injury: An experimental canine model. Am J Gastroenterol 2004;99:2098–106.
174. Tuchman DN, Boyle JT, Pack AI, et al. Comparison of airway responses following tracheal or esophageal acidification in the cat. Gastroenterology 1984;87:872–81.
175. Cuttitta G, Cibella F, Visconti A, et al. Spontaneous gastro-esophageal reflux and airway patency during the

night in adult asthmatics. Am J Respir Crit Care Med 2000;161:177–81.
176. El-Serag HB, Lee P, Buchner A, et al. Lansoprazole treatment of patients with chronic idiopathic laryngitis: A placebo-controlled trial. Am J Gastroenterol 2001;96:979–83.
177. Noordzij JP, Khidr A, Evans BA, et al. Evaluation of omeprazole in the treatment of reflux laryngitis: A prospective, placebo-controlled, randomized, double-blind study. Laryngoscope 2001;111:2147–51.
178. Vaezi MF, Richter JE, Stasney CR, et al. A randomized, double-blind, placebo-controlled study of acid suppression for the treatment of suspected laryngopharyngeal reflux. Gastroenterology 2004;126(suppl 2):A22.
179. Sontag S, O'Connell S, Khandelwal S, et al. Most asthmatics have gastro-esophageal reflux with or without bronchodilator therapy. Gastroenterology 1990;99:613–20.
180. Harding S, Kiljander T, Field S, et al. Efficacy of esomeprazole 40 mg twice daily for 16 weeks in adults with asthma: A randomized placebo-controlled trial. Gastroenterology 2005;128 (suppl 2):A-61.
181. Havas T, Huang S, Levy M, et al. Posterior phayrngolaryngitis, double-blind randomized placebo-controlled trial of proton pump inhibitor therapy. Aust J Otolaryngol 1999;3:243–6.
182. Eherer AJ, Habermann W, Hammer HF, et al. Effect of pantoprazole on the course of reflux-associated laryngitis: A placebo-controlled double-blind crossover study. Scand J Gastroenterol 2003;38:462–7.
183. Allen CJ, Anvari M. Does laparoscopic fundoplication provide long-term control of gastro-esophageal reflux related cough? Surg Endosc 2004;18:633–7.
184. Ekstrom T, Lindgren BR, Tibbling L. Effects of ranitidine treatment on patients with asthma and a history of gastro-esophageal reflux: A double blind crossover study. Thorax 1989;44:19–23.
185. Goodall RJR, Earis JE, Cooper DN, et al. Relationship between asthma and gastro-esophageal reflux. Thorax 1981;36:116–21.
186. Nagel RA, Brown P, Perks WH, et al. Ambulatory pH monitoring of gastro-esophageal reflux in 'morning dipper' asthma. BMJ 1988;297:1371–3.
187. Gustafsson PM, Kjellman N-IM, Tibbling L. A trial of ranitidine in asthmatic children and adolescents with or without pathological gastro-esophageal reflux. Eur Respir J 1992;5:201–6.
188. Ford GA, Oliver PS, Prior JS, et al. Omeprazole in the treatment of asthmatics with nocturnal symptoms and gastro-esophageal reflux: A placebo controlled crossover study. Postgrad Med J 1994;70:350–4.
189. Teichtahl H, Kronborg IJ, Yeomans ND, et al. Adult asthma and gastro-esophageal reflux: The effect of omeprazole therapy on asthma. Aust N Z J Med 1996;26:671–6.
190. Meier JH, McNally PR, Punja M, et al. Does omeprazole (Prilosec) improve respiratory function in asthmatics with gastro-esophageal reflux? A double-blind placebo-controlled crossover study. Dig Dis Sci 1994;39:2127–33.
191. Böcskei C, Viczián M, Böcskel R, et al. The influence of gastro-esophageal reflux disease and its treatment on asthmatic cough. Lung 2005;183:53–62.
192. Munoz JV, Herreros B, Sanchiz V, et al. Dental and periodontal lesions in patients with gastro-esophageal reflux disease. Dig Liver Dis 2003;35:461–7.
193. Bohmer CJ, Klinkenberg-Knol EC, Niezen-de Boer MC, et al. Dental erosions and gastro-esophageal reflux disease in institutionalized intellectually disabled individuals. Oral Dis 1997;3:272–5.
194. Schroeder PL, Filler SJ, Ramirez B, et al. Dental erosions and acid reflux disease. Ann Intern Med 1995;122:809–15.
195. Weaver EM. Association between gastro-esophageal reflux and sinusitis, otitis media, and laryngeal malignancy: A systematic review of the evidence. Am J Med 2003;115:81S–9S.
196. Groen JN, Smout AJPM. Supra-oesophageal manifestations of gastro-esophageal reflux disease. Eur J Gastroenterol Hepatol 2003;15:1339–50.
197. El-Serag HB, Gilger M, Kuebeler M, et al. Extraesophageal associations of gastro-esophageal reflux disease in children without neurologic defects. Gastroenterology 2001;121:1294–9.
198. Graf K-I, Karaus M, Heinemann S, et al. Gastro-esophageal reflux in patients with sleep apnea syndrome. Z Gastroenterol 1995;33:689–93.
199. Heinemann S, Graf K-I, Karaus M, et al. Untersuchungen über das Auftreten einer obstruktiven schlafbezogenen Atmungsströrung in Zusammenhang mit einer gastro-öesophagealen Refluxerkrankung. Pneumologie 1995;49(suppl 1):S139-41.
200. Teramoto S, Ohga E, Matsui H. Obstructive sleep apnea syndrome may be a significant cause of gastro-esophageal reflux disease in older people. J Am Geriatr Soc 1999;47:1273–4.
201. Valipour A, Makker HK, Hardy R, et al. Symptomatic gastro-esophageal reflux in subjects with a breathing sleep disorder. Chest 2002;121:1748–53.
202. Guda N, Partington S, Vakil N. Symptomatic gastro-esophageal reflux, arousals and sleep quality in patients undergoing polysomnography for possible obstructive sleep apnoea. Aliment Pharmacol Ther 2004;20:1153–9.
203. Field SK, Flemons WW. Is the relationship between obstructive sleep apnea and gastro-esophageal reflux clinically important? Chest 2002;121:1730–3.
204. Berg S, Hoffstein V, Gislason T. Acidification of distal esophagus and sleep-related breathing disturbances. Chest 2004;125:2001–106.
205. Morse CA, Quan SF, Mays MZ, et al. Is there a relationship between obstructive sleep apnea and gastro-esophageal reflux disease? Clin Gastroenterol Hepatol 2004;2:761–8.

All member of the consensus group were paid an honorarium for their participation by Astra -Zeneca Research and Development.

Guarantor of the article: Nimish Vakil
Development of statements: All
Delphi Process, Global definition and classification: Nimish Vakil
Esophageal Syndromes, Symptomatic: Roger Jones
Syndromes with esophageal injury (reflux esophagitis and stricture): Sender van Zanten
Syndromes with esophageal injury (barrets esophagus and adenocarcinoma): John Dent
Integration of text and development of figures: Nimish Vakil
Financial support: Astra-Zeneca research and Development
Potential competing interests: None