

CME

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

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- 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.

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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

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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.*, $\geq 67\%$) 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 Astra-Zeneca 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 $\geq 67\%$ 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

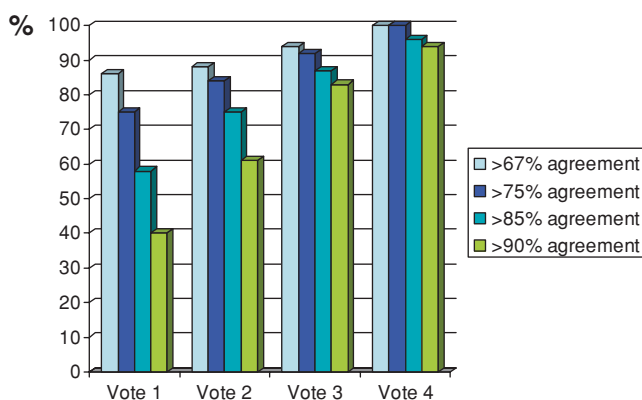


Figure 1. Percentage of statements at each level of agreement at each vote.

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, impedance 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 ap-

proach 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

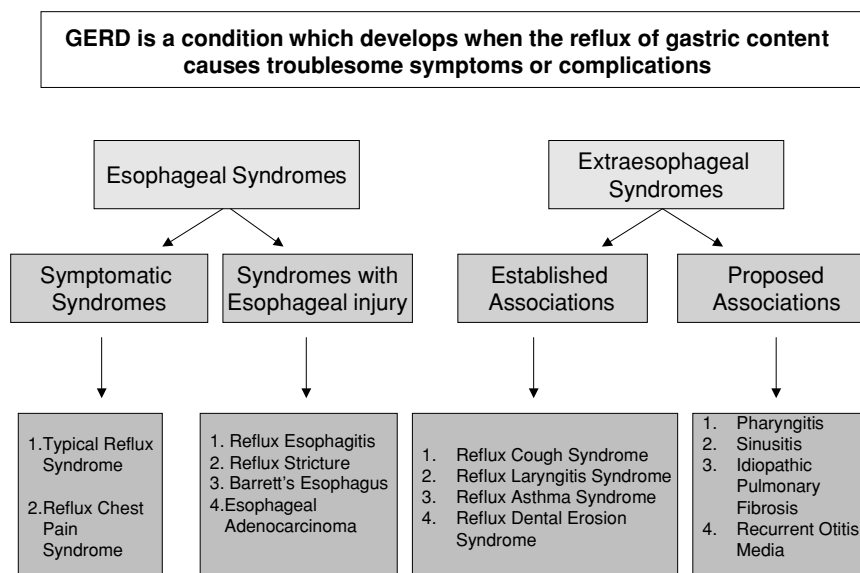


Figure 2. The overall definition of GERD and its constituent syndromes.

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), H₂-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 au-

thors 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,

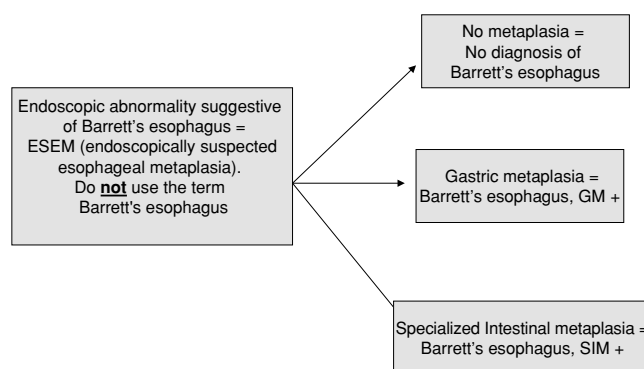


Figure 3. Consensus terminology for Barrett's esophagus.

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).

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 H₂-receptor antagonist therapy for chronic cough showed no therapeutic benefit (161). Several uncontrolled trials on H₂-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.

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