

Diagnosis and Management of Non-Erosive Reflux Disease – The Vevey NERD Consensus Group

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Key Words

Delphi method · Gastro-esophageal reflux disease · NERD, clinical features · NERD, definition · NERD, diagnosis and treatment · NERD, disease assessment · Non-erosive reflux disease (NERD) · Vevey NERD Consensus Group

Abstract

Background/Aims: Although considerable information exists regarding gastroesophageal reflux disease with erosions, much less is known of non-erosive reflux disease (NERD), the dominant form of reflux disease in the developed world. **Methods:** An expert international group using the modified Delphi technique examined the quality of evidence and established levels of agreement relating to different aspects of NERD. Discussion focused on clinical presentation, assessment of clinical outcome, pathobiological mechanisms, and clinical strategies for diagnosis and management. **Results:** Consensus was reached on 85 specific statements. NERD was defined as a condition with reflux symptoms in the absence of mucosal lesions or breaks detected by conventional endoscopy, and without prior effective acid-suppressive therapy. Evidence supporting this

diagnosis included: responsiveness to acid suppression therapy, abnormal reflux monitoring or the identification of specific novel endoscopic and histological findings. Functional heartburn was considered a separate entity not related to acid reflux. Proton pump inhibitors are the definitive therapy for NERD, with efficacy best evaluated by validated quality-of-life instruments. Adjunctive antacids or H₂ receptor antagonists are ineffective, surgery seldom indicated. **Conclusions:** Little is known of the pathobiology of NERD. Further elucidation of the mechanisms of mucosal and visceral hypersensitivity is required to improve NERD management.

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Introduction

Gastroesophageal reflux disease (GERD) develops when the reflux of gastric contents into the esophagus leads to troublesome symptoms, with or without mucosal damage, and/or complications [1]. GERD is common and the prevalence, as defined by at least weekly heartburn and/or acid regurgitation, is estimated to range from 10 to 20% in Western countries and is about 5% in Asian countries [2]. GERD adversely affects health-related quality of life (QoL) [3], and the majority of patients (~60%) with typical reflux symptoms have no evidence of erosive esophagitis at endoscopy [4]. Such patients are usually considered to have non-erosive reflux disease (NERD) [5].

The majority of patients with symptomatic reflux are managed in the community by their family physician who typically prescribes empiric acid suppression treatment with a proton pump inhibitor (PPI) and without knowledge of the endoscopic appearances of the esophageal mucosa. Referral to a specialist is usually reserved for those with alarm symptoms or those who do not obtain an adequate response to PPI therapy. Thus, for the practicing non-gastroenterologist clinician, the diagnosis of NERD (which, by definition, requires endoscopy) is not intuitive. Moreover, the findings of ultrastructural changes associated with acid-related damage suggest that NERD might be part of a continuum with erosive reflux disease (ERD), adding further to semantic confusion.

To address these and other relevant questions about NERD, a Consensus Conference was held at Vevey, Switzerland, from November 30 to December 2, 2007. This was a multidisciplinary workshop which involved participants from around the world. Following a plenary session with several state-of-the-art talks, participants were split into four workshops which addressed: (1) clinical presentation, (2) trial methodology, (3) pathobiology, and (4) diagnosis and treatment.

Methodology

Consensus was achieved using a modified Delphi process [1, 6]. A consensus group was selected on the basis of discipline, expertise and geographical region. 37 participants were selected from North America, South America, Western Europe, Eastern Europe, Central Asia, South East Asia, and Australia. They were chosen to represent all major disciplines involved in the care of NERD patients: gastroenterology, surgery, primary care, and pathology. They also had a broad range of methodology expertise including translational research related to the pathophysiology of NERD (e.g. acid reflux, hypersensitivity, motility, functional neuroimaging), clinical trials, epidemiology and systematic reviews. A core group was se-

lected to develop questions to be voted on and the consensus group further modified the questions that would be addressed during the workshop. 85 questions were compiled and each expert was given at least two questions to research for the meeting. Systematic reviews were conducted to identify all the relevant research for each question. English language articles were selected from Embase and Medline from 1980 to September 2007. The evidence was reviewed by the expert assigned to a particular question who chose the data that was relevant for the meeting. It was noted that a particular challenge in reviewing the literature was the desire to exclude data on patients with 'functional heartburn' wherever possible, in accord with the view that such patients are outside the GERD spectrum [5]. However, in much of the existing literature on NERD, the inclusion criteria are poorly defined and the data likely 'muddied' by the inclusion of patients with functional heartburn.

At the consensus meeting the experts were divided into four groups to discuss four broad areas of applicable to NERD. The groups further refined the questions and voted on the statements. Two groups merged and repeated the process, focusing on questions that were felt to be controversial. Finally, all experts met to vote at the end of the meeting. Voting used a 6-point Likert scale: (1) agree strongly, (2) agree with minor reservation, (3) agree with major reservation, (4) disagree with minor reservation, (5) disagree with major reservation, and (6) disagree strongly. Consensus was defined a priori as $\geq 80\%$ agreeing strongly or with minor reservation with a statement. All voting was anonymous via a keypad. After the meeting, two further votes were conducted by e-mail. Votes were anonymized and collated. After the third iteration no further consensus was achieved and the process was terminated.

The strength of the evidence was also classified according to the GRADE system [7]. Quality was graded as high (future research very unlikely to change the estimate of effect), medium (future research may change the estimate of effect), low (future research very likely to change the estimate of effect), and very low (any estimate of effect very uncertain).

Definition of NERD

1. NERD is a subcategory of GERD characterized by troublesome reflux-related symptoms in the absence of esophageal mucosal erosions/breaks at conventional endoscopy and without recent acid-suppressive therapy. 100% agree. Grade of evidence = N/A

Most patients (~60%) with typical reflux symptoms have no evidence of erosive esophagitis at endoscopy. These patients are usually considered to have NERD, particularly if there is supportive evidence that their symptoms are due to acid reflux – for example a positive correlation between the symptoms and abnormal acid exposure on 24-hour ambulatory pH measurement or evidence of a symptomatic response to therapeutic acid suppression. However, the spectrum of NERD should not include patients with 'functional heartburn' (normal endoscopy, and no correlation of symptoms with acid exposure),

which is not associated with acid reflux and should be excluded from the GERD spectrum according to the Rome III criteria [8].

Clinical Features of NERD

2. Patients with upper gastrointestinal symptoms, unrelated to reflux of gastric contents, are excluded from NERD. **95% agree. Grade of evidence = N/A**

3. A diagnosis of NERD is unlikely in a patient with heartburn and a normal endoscopy who fails to obtain appropriate symptom relief with a PPI and who has normal esophageal acid exposure and a negative symptom association. **95% agree. Grade of evidence = Low**

The dominance of acidic reflux in the etiology of the symptoms of NERD is underlined by the widespread agreement among participants that if the patient's symptoms do not respond to acid suppression medication or cannot be proven to be associated with an esophageal acid exposure on pH testing, then the diagnosis of NERD is unlikely. However, the presence of gas in the refluxate may well enhance reflux perception in NERD patients with 'physiological' esophageal acid exposure [9]. There was strong agreement to endorse the view of the 'Rome' group that patients with functional heartburn (normal endoscopy, and no correlation of symptoms with acid exposure) should be excluded from the GERD spectrum [8].

4. The prevalence of GERD is increasing. **95% agree. Grade of evidence = Moderate**

5. The prevalence of NERD is increasing. **81% agree. Grade of evidence = Low**

6. The increasing BMI contributes to the increasing prevalence of NERD. **78% agree. Grade of evidence = Very low**

NERD is the major subcategory of GERD, a condition that in some Western populations has reached epidemic proportions. NERD is probably increasing at least as fast as its 'parent' GERD, though it was appreciated that there was little direct evidence to support this assertion [10]. The increase in GERD parallels the increase in obesity in developed nations [11], but the group just failed to support the statement that BMI is contributing to an increase in NERD, principally due to a paucity of research addressing this issue.

7. Symptom severity does not allow confident differentiation between NERD and ERD. **100% agree. Grade of evidence = Moderate**

8. There is no specific symptom pattern that reliably predicts the diagnosis of NERD as compared to ERD. **97% agree. Grade of evidence = Moderate**

9. It is not known whether or not nocturnal reflux symptoms are less prevalent in NERD than ERD. **97% agree. Grade of evidence = N/A**

10. The impact of reflux symptoms on QoL in NERD patients is as important as in those with ERD. **100% agree. Grade of evidence = Low**

There was strong consensus at the conference that the range and severity of symptoms experienced in NERD are similar to those of ERD, and that symptoms were not at all reliable predictors of findings at endoscopy. Indeed, population-based endoscopic surveys have revealed esophageal erosions in many patients without any GERD symptoms [4].

Whether or not nocturnal reflux symptoms are less prevalent in NERD than they are in ERD is currently unknown and worthy of future study. For individual patients, the presence or absence of erosions may not be of much relevance in symptom generation, since all participants agreed that the impact of the reflux symptoms on QoL appears as substantial in NERD patients as it is in patients with ERD [12].

11. The prevalence of concomitant functional dyspepsia and/or IBS is higher in NERD than in ERD. **92% agree. Grade of evidence = Moderate**

Patients with NERD often have other functional gastrointestinal symptoms, such as functional dyspepsia and irritable bowel syndrome, with a frequency higher than that observed in most studies of ERD [13–15]. A common denominator may well be visceral hypersensitivity [16].

12. In the elderly (>60 years) with reflux symptoms, NERD is less prevalent than ERD. **62% agree. Grade of evidence = Moderate**

The group felt that there was a dearth of data on whether NERD was relatively less common than ERD in the elderly, which is why this statement was rejected.

13. Prior self-medication with antacids does not interfere with the endoscopic detection of esophageal erosions. **89% agree. Grade of evidence = Moderate**

14. *The effect of prior self-medication with alginates on the endoscopic detection of esophageal erosions has not been studied.* **97% agree. Grade of evidence = Moderate**

15. *Recent self-medication with H₂RAs or PPIs can interfere with the endoscopic detection of esophageal erosions.* **100% agree. Grade of evidence = High**

The categorization of a patient with reflux symptoms into NERD versus ERD can, of course, only be made after endoscopy. Thus, one of the key difficulties in defining the prevalence of NERD is that many endoscopies are now performed in patients who are taking or have recently taken acid-suppressive medications. There was unanimous agreement among meeting participants that recent self-medication with PPIs or H₂RAs can interfere with erosion detection at endoscopy. A Cochrane systematic review has shown that both PPIs and H₂RA therapy are effective at healing esophagitis [17] and, once healed, up to 20% of participants remain in remission after 1 year of follow-up [18]. In contrast, a systematic review of the literature suggested that antacids alone have no effect in healing esophagitis. There are no randomized controlled trials evaluating whether alginates heal erosive esophagitis. Since many patients with GERD symptoms have taken PPIs or histamine H₂ receptor antagonists prior to endoscopy, much of what is now considered NERD may in fact be previously treated ERD. This issue reflects the difficulty that many physicians have in dealing with the precise nature of the relationship between the two entities and whether they constitute separate or linked disease phenomena.

16. *In NERD patients, the symptom pattern does not allow prediction of development of ERD.* **97% agree. Grade of evidence = Low**

17. *An objective marker to distinguish reflux disease from functional heartburn is an unmet need.* **97% agree. Grade of evidence = N/A**

18. *In the majority of patients with NERD the disease does not progress to ERD.* **92% agree. Grade of evidence = Low**

In the majority of patients it is impossible to predict from symptoms whether or not erosions will be present at endoscopy. An objective marker that could somehow distinguish reflux disease from functional heartburn was therefore felt to be highly desirable, though presently far from a reality. Most participants agreed that based on current data NERD does not progress to erosive disease in the majority of patients [19], though further well-de-

signed studies in this area would be of value, and the view that these are distinct entities is actively disputed [20–22].

Disease Assessment for NERD Studies

19. *Parallel-group studies are preferred to cross-over designs in clinical trials of NERD therapy.* **95% agree. Grade of evidence = Moderate**

20. *Studies assessing outcomes need to compare an intervention with an alternative or placebo.* **97% agree. Grade of evidence = Moderate**

The gold standard method of evaluating treatment is the randomized controlled trial [23]. This can either be a cross-over or parallel-group design. There was a clear vote in favor of parallel-group randomized trials because cross-over trials require that there is little carryover effect of the intervention and that the disease is stable over time [24]. Neither of these requirements applies to NERD where symptoms fluctuate and, although some patients relapse quickly once acid suppression is discontinued, response to therapy can last weeks to months with 21% remaining in remission after 6–12 months of follow-up [18]. The group also strongly supported the statement that an intervention needs to be compared with a placebo or an alternative therapy. Reports of cohorts of NERD patients responding to a drug without such comparisons are difficult to interpret as any result could be due to regression to the mean or a placebo effect.

21. *Validated reflux symptom questionnaires must be used in clinical trials of NERD where symptoms are an outcome.* **97% agree. Grade of evidence = Low**

22. *Symptom response to therapy should be assessed by daily diaries over a period of 7 days prior to patient assessment.* **84% agree. Grade of evidence = Low**

23. *Symptom response needs to be predefined and the primary outcome should be the resolution of symptoms.* **95% agree. Grade of evidence = Moderate**

Usually the most clinically important outcome of NERD trials is the response of symptoms to therapy. The group supported the use of validated reflux symptom questionnaires [25] to assess this outcome. Ideally the questionnaire should be psychometrically tested, internally consistent, valid, reliable and responsive to change, but often validated questionnaires only meet some of these criteria [25, 26]. When administering the question-

naire, patient-reported outcomes are preferable to those completed by the investigator as research suggests clinicians underestimate the severity of a patient's symptoms [27]. In theory, daily diaries are an optimal method of capturing patient-reported outcomes so that problems with recall are minimized [28]. The period over which daily diaries should be administered is uncertain. Seven days was chosen for pragmatic reasons, and whilst this will often be the most appropriate period of assessment, there may be reasons why shorter or longer durations of assessment of therapy may be used. Although the group voted in favor a 7-day daily diary for research trials, the uncertainty around the optimal time period is reflected in the lower percentage agreement for this statement than for the other statements in this section. The group also recommended that the primary outcome should be pre-specified and preferably this should be the resolution of reflux symptoms. This is based on a systematic review of esophagitis trials where resolution of symptoms correlated well with healing of esophagitis, whereas improvement of symptoms overestimated treatment effect [29].

24. Evaluating NERD patients with other overlapping gastrointestinal syndromes may facilitate the identification of subgroups that are less responsive to treatment. 92% agree. Grade of evidence = Moderate

25. Evaluating NERD patients with overlapping non-cardiac chest pain or extraesophageal syndromes may facilitate the identification of patients who are less responsive to treatment. 92% agree. Grade of evidence = Low

26. The timing of symptoms (constant, day and night or meal-related) needs to be evaluated to identify patients who respond differently to treatment. 78% agree. Grade of evidence = Very low

A cross-sectional survey of secondary care patients presenting with heartburn found that patients with esophagitis had a greater prevalence of coexisting hiatus hernia and evidence of higher esophageal acid exposure compared with NERD patients. In contrast, NERD patients were more likely to have irritable bowel symptoms, psychological disorders and a positive acid perfusion test [30], and these findings have been confirmed by others [31, 32]. The significant overlap between NERD and other functional disorders suggests patients may have hypersensitivity to acid [30], dysmotility or possibly central processing problems. Such patients may be more difficult to treat with conventional therapies – this hypothesis needs prospectively testing in trials. Traditionally, trials of NERD have not assessed such concomitant issues or

have excluded them from the study. There was a strong feeling within the group that these questions need evaluating, so it is important to study NERD patients with and without overlapping functional disorders to see if there are different responses to therapy. Consensus was also achieved for the proposition to study NERD patients with concomitant non-cardiac chest pain or extraesophageal syndromes, for similar reasons. There are few published studies that have evaluated these patients, but one randomized trial of a PPI versus placebo in non-cardiac chest pain reported that those with significant heartburn were less likely to respond to therapy than those without heartburn and it was only in the latter group that there was a statistically significant response to acid suppression [33]. It is paradoxical results like this that emphasize the need to study NERD patients with and without overlapping functional syndromes.

It was also considered important to measure the timing of symptoms in NERD. Approximately 50% of GERD patients have disturbed sleep due to reflux symptoms [34] and data suggest that the degree of day- and nighttime acid reflux may be different in NERD patients compared to those with esophagitis [35].

27. Disease-specific and general QoL measurements in NERD therapy studies are important. 97% agree. Grade of evidence = Moderate

28. Patient satisfaction evaluation in NERD studies is an important outcome measure. 92% agree. Grade of evidence = N/A

QoL can be assessed using a disease-specific instrument which will be more sensitive to the effects of therapy, though the results cannot be directly compared across non-gastrointestinal diseases [36]. Alternatively, a generic QoL instrument can be used. This allows the impact of therapy in NERD to be compared with therapies for other diseases, although the sensitivity of these questionnaires is less than for disease-specific instruments. Patient satisfaction with treatment is another important outcome that is rarely measured [37]. The paucity of data in this area needs to be addressed. Indeed, information regarding patient satisfaction may be particularly valuable when reflux symptoms cannot be meaningfully applied as primary outcome measures, for example in the evaluation of 'on-demand therapy' in NERD trials [38]. Patient satisfaction is a multidimensional outcome that also depends on patient expectations. Ideally this should also be evaluated using a validated questionnaire [39].

29. NERD patients who are included in clinical trials should have at least moderate reflux symptoms for 3 months. **95% agree. Grade of evidence = Low**

30. NERD patients who are included in clinical trials should have at least moderate reflux symptoms more than once per week. **95% agree. Grade of evidence = Low**

Patients entering into trials should have sufficient severity of symptoms so that any benefit of therapy can be adequately captured. There was broad agreement that patients should have at least moderate symptoms at least once a week, for 3 months or longer. Transient reflux symptoms are common in the community and do not need treatment other than lifestyle advice and antacid therapy. It is only patients with chronic symptoms who should be evaluated for their response to more specific treatment. At least 3 months of symptoms was considered to indicate chronicity, in keeping with Rome III definitions [5]. The group felt that symptoms needed to be present more than once per week to be consistent with the requirement that daily diaries needed to be kept for at least 1 week (as decided earlier in this section).

31. NERD clinical trials that aim to further characterize the population that respond to therapy should include pH and/or impedance studies. **87% agree. Grade of evidence = Moderate**

32. NERD patients undergoing pH and impedance monitoring should have symptom-associated analysis of reflux events. **97% agree. Grade of evidence = Moderate**

33. Impedance and/or pH monitoring is important to study in patients whose symptoms do not respond to PPI therapy. **95% agree. Grade of evidence = Very low**

Patients enrolled in NERD trials may not respond for a number of reasons. Non-responders may have symptoms due to acid reflux but have suboptimal acid suppression therapy, or they may have non-acid reflux and, hence, no response to acid suppression therapy. Alternatively, their symptoms may not be due to reflux at all [40, 41]. Characterizing these groups may help predict patients who are likely to respond to therapy and therefore evaluation of acid reflux events through pH monitoring and also non-acid reflux through impedance testing is important in NERD trials [42]. Simply documenting the occurrence of reflux events is not sufficient, because these may not necessarily be the cause of the patient's symptoms [43]. The most rigorous approach to evaluating whether symptoms are due to reflux episodes is to calculate the symptom association probability by recording

the presence and absence of reflux and symptom events every 2 min as a 2×2 contingency table. A χ^2 test is then used to determine whether any correlation is due to chance [44]. Studies have suggested that the symptom association probability predicts patients who will respond to PPI therapy. However, this approach is far from perfect and there is a paucity of trials evaluating patients who do not respond to acid suppression.

34. Novel endoscopic and biopsy-based abnormalities are insufficiently validated to be used as primary outcome measures in clinical trials. **95% agree. Grade of evidence = Low**

35. If novel endoscopic and/or histologic endpoints are investigated images should be independently scored to objectively evaluate reproducibility. **95% agree. Grade of evidence = Moderate**

36. Biopsy-based methods (optical and tissue) need to specifically define sites of biopsies and methods used to process tissue. **95% agree. Grade of evidence = Moderate**

37. In NERD clinical trials the assessment of novel endoscopic and biopsy based features should be performed at baseline and following therapy. **78% agree. Grade of evidence = Very low**

A variety of novel endoscopic and biopsy-based methods have been evaluated in NERD in an attempt to detect subtle mucosal abnormalities that cannot be seen with standard white light imaging. Although magnification endoscopy has not identified any such abnormalities [45], chromoendoscopy with Lugol's iodine solution has revealed unstained streaks in the distal esophagus more often in GERD patients than in controls [46]. These chromoendoscopic findings were not detected by conventional white light endoscopy and were associated with increased basal cell thickness and increased papillary height compared with the unstained areas of the esophagus. A landmark study by Sharma et al. [47] evaluated narrow band imaging in patients with erosive esophagitis, NERD and in a control population. Narrow band imaging in conjunction with zoom magnification revealed several unique findings not previously described in the NERD patients compared to the controls, including increased number, tortuosity and dilation of intrapapillary capillary vessels, microerosions, and increased vascularity at the squamocolumnar junction. Finally, Kiesslich et al. [48] have provided preliminary data on the use of confocal endomicroscopy in NERD. In 30 symptomatic GERD patients, the features of >5 capillary loops

and dilated intercellular space $\geq 7 \mu\text{m}$ as defined by confocal endomicroscopy had a sensitivity of 95% and a specificity of 85.4% compared to conventional histological findings in GERD.

Histological findings have also been addressed in NERD. These include basal zone hyperplasia, papillary elongation, inflammatory infiltrates and dilated intercellular spaces. There are significant limitations with each of these criteria, as recently described [49, 50]. However, dilation of intercellular spaces is consistently found more often in NERD patients than in controls. Importantly, intercellular space dilation improves after treatment with acid suppression. To date, most of the work on dilated intercellular spaces has required electron microscopy to measure the width of intercellular spaces. Different studies have defined dilation variably. Furthermore, intercellular space diameter is greater in the distal esophagus than the proximal esophagus in both NERD and erosive esophagitis patients [51]. Unfortunately, electron microscopy is not a practical technique for clinical application.

Thus despite the interest in novel endoscopic and histological markers of NERD, the meeting participants felt that none was sufficiently characterized to be used as a primary outcome in drug therapy trials of NERD and that the interpretation of any changes seen would be difficult to interpret according to current knowledge. This is an evolving area and it is anticipated that future studies may yield more sensitive and specific features of NERD.

To date there has been little standardization of biopsy techniques or tissue processing in GERD and NERD patients. Biopsies have been obtained at the squamocolumnar junction, or at 1, 2, 3 and 5 cm above it. Furthermore, there is no consensus on the number of biopsy specimens obtained, or the location around the inner circumference of the esophagus at which biopsies should be taken. (For example, should they be taken from each of the four quadrants, a specific quadrant or at random?) This issue is especially important since the severity of exposure to refluxate decreases with increasing distance from squamocolumnar junction and the distribution of mucosal injury may be patchy. The group was therefore strongly in favor of carefully recording the site from which the biopsies are taken in future endoscopic studies of NERD.

There is little data regarding the appropriate duration of therapy necessary to evaluate the resolution of endoscopic and histologic abnormalities in patients with NERD. Dilated intercellular spaces, as determined by electron microscopy, have been evaluated before and after 12 weeks of therapy with omeprazole [52]. Dilated intercellular spaces were reported to have resolved in 20

of 22 NERD patients. However, no measurements were made prior to 12 weeks, so we do not know if these changes resolved earlier. Similarly, limited data are available on the effect of therapy on any novel endoscopic imaging techniques used in NERD, such as high-resolution or high-definition white light endoscopy, magnification endoscopy, chromoendoscopy, narrow band imaging or confocal laser endomicroscopy. One small study of magnification endoscopy found that 4 weeks of esomeprazole decreased the endoscopic changes in NERD patients [53]. Thus, the optimal duration of therapy necessary to evaluate novel imaging and histologic techniques is unknown. Most likely, 4 weeks should be considered a minimum, but 12 weeks or more of therapy may be warranted and the meeting attendees were unable to reach consensus as to whether endoscopic and biopsy changes seen in NERD should be measured at baseline and after therapy.

38. Adjunctive investigations (such as autonomic tests, functional imaging and pain thresholds) provide useful data on NERD subgroups. 68% agree. Grade of evidence = Very low

Autonomic abnormalities have been reported in both ERD and NERD patients [54, 55]. A study by Shapiro et al. [32] found no differences in baseline autonomic function between functional heartburn and NERD patients. However, patients with functional heartburn demonstrated a higher increase in heart rate and skin conductance after acid perfusion, compared to NERD [32]. Brain functional imaging has not been tested either before or after treatment in NERD patients. Overall the group felt there was insufficient evidence to recommend adjunctive tests as a method of identifying patients who will respond to therapy.

Pathobiological Mechanisms

39. Acidity of the refluxate is the most important cause of symptom generation in NERD. 87% agree. Grade of evidence = High

40. Weakly acidic reflux contributes to generation of symptoms in NERD. 87% agree. Grade of evidence = Low

There was strong agreement as to the role of acid as a cause of symptoms, based on evidence of symptom generation in patients with symptomatic reflux and a positive Bernstein test [56]. In that study, all subjects experi-

enced pain with pH 1 and 1.5 solutions delivered to the distal esophagus, 80% had pain with the pH 2.0 solution, and half had pain with solutions of pH 2.5–6. Time-to-pain onset also statistically significantly increased with increasing pH ($p < 0.001$). Weakly acidic reflux (pH 4–7, detected by impedance pH metry) is associated with regurgitation and atypical GERD symptoms [57]. Short exposure of esophageal mucosa to bile acid in acidic and weakly acidic conditions can impair mucosal integrity in an experimental model [58] and is likely to contribute to symptom generation [59]. Although not discussed specifically at the meeting, pepsin can exacerbate mucosal damage [60], but whether pepsin or pancreatic enzymes can elicit symptoms is not known.

41. *Mechanoreceptor-mediated pathways are involved in symptom generation in NERD. 80% agree. Grade of evidence = N/A*

42. *Different types of receptors are involved in the generation of reflux-induced symptoms in NERD. 95% agree. Grade of evidence = N/A*

43. *Peripheral and/or central mechanisms of hypersensitivity contribute to symptom generation in NERD. 95% agree. Grade of evidence = N/A*

Peripheral and central mechanisms of hypersensitivity have been recognized to contribute to symptom generation in NERD. Several types of mechano- and chemoreceptors have been identified as overexpressed and activated in NERD, including the vanilloid receptor TRPV1 and the protease-activated receptor PAR-2 [61]. Diverse chemical and mechanical receptors are most likely involved in mediating reflux-associated symptoms, including those that respond to esophageal acid, distension and possibly other stimuli. Indeed, hypersensitivity to balloon distension, presumably mediated by mechanoreceptors, is a more common finding in NERD than in erosive esophagitis [62]. Symptoms in NERD are also likely augmented through peripheral and central hypersensitivity to these same stimuli in patients with NERD, as in non-cardiac chest pain. Visceral hypersensitivity of the esophagus is mediated by serotonin- and adenosine-dependent neural transmission [63, 64–67], thus supporting a role for anxiety and other as yet undefined psychological factors in the generation or amplification of NERD symptoms.

44. *pH monitoring permits the evaluation of the relationship between acid reflux and symptom events in NERD. 92% agree. Grade of evidence = N/A*

45. *Combined pH and impedance monitoring is superior to pH monitoring alone in establishing the relationship between reflux events and symptom generation in NERD. 95% agree. Grade of evidence = N/A*

46. *Currently available techniques for intraesophageal bile measurement are not adequate for establishing the relationship between reflux events and symptom generation in NERD. 97% agree. Grade of evidence = N/A*

The American College of Gastroenterology guidelines for esophageal reflux testing outline the appropriate use of pH monitoring in the management of GERD and also address measurement of impedance and bile reflux [68]. In one study examining esophageal acid exposure and symptoms, almost 50% of symptomatic reflux episodes occurred after meals, especially after a non-standardized compared with a standardized meal. Symptomatic episodes tended to last longer and to occur in the supine position. Six percent of reflux episodes were temporally associated with typical GERD symptoms. This association seemed to be influenced by the acidity of the refluxate [69]. Combining impedance with pH monitoring improves diagnosis reduces the proportion of NERD patients classified as having ‘functional heartburn’ [70]. Bile reflux measurements are currently not considered to be valid for symptom exploration.

In spite of the progress in technology, the temporal association of acid reflux events is often not concordant with symptoms. This suggests that reflux episodes may condition the esophageal mucosa for nociception and increase its susceptibility to relatively minor chemical or distension stimuli.

47. *Mucosal and salivary secretion are involved in the pathogenesis of NERD. 37% agree. Grade of evidence = N/A*

48. *Esophageal peristalsis and clearance are not established as being abnormal in NERD. 100% agree. Grade of evidence = N/A*

49. *Altered gastric emptying does not contribute to the pathogenesis of NERD. 58% agree. Grade of evidence = Very low*

50. *Helicobacter pylori infection is not involved in the pathogenesis of NERD. 86% agree. Grade of evidence = moderate*

Surprisingly, in view of the standard teaching on GERD pathophysiology, no major esophageal or gastric motor abnormalities are detectable in patients with NERD. No difference was found between NERD and

mild to moderate ERD in terms of acid exposure time and esophageal motor abnormalities [71]. Moreover, there was general agreement that there was no consistent evidence for abnormalities of gastric emptying, of salivary secretions or esophageal mucosal secretions in the pathogenesis of NERD.

The role of *H. pylori* infection in GERD has been debated for more than a decade, but critical evaluation of the data concludes that the role of *H. pylori* infection is neither considered to be causative nor protective in NERD [72]. In 6,125 patients with GERD, the prevalence of *H. pylori* in those with NERD was ~25% and not significantly different from patients with ERD or Barrett's [73].

51. Anxiety and other psychological factors contribute to symptoms in NERD. 89% agree. Grade of evidence = Low

There was a high level of agreement with the assertion that psychological factors, in particular anxiety, contributed to symptom generation in NERD, even though the quality of evidence in this area was acknowledged to be low and confounded by the inclusion of patients who meet the definition of functional heartburn. However, several recent studies have addressed psychological factors and anxiety in patients with reflux disease. For example, in a cohort study, psychological distress was present in 41% of 101 reflux patients and this predicted worse reflux symptoms and worse QoL both before and after PPI treatment [74].

52. Dilated intercellular spaces are a consequence of reflux injury in NERD. 84% agree. Grade of evidence = Low

53. Dilated intercellular spaces can be studied by electron microscopy and by light microscopy. 95% agree. Grade of evidence = Low

54. Dilated intercellular spaces are restored with acid-suppressive therapy. 78% agree. Grade of evidence = Very low

As discussed in the section on disease assessment above, there is considerable interest in investigating ultrastructural, microscopic or advanced endoscopic markers of GERD in patients with no evident abnormality by conventional endoscopy. The most prominent morphological abnormalities described thus far are dilated intercellular spaces. These are most reliably characterized by electron microscopy but are also detectable with light microscopy. The dilated intercellular spaces occur preferentially in the stratum below the surface squamous epi-

thelium and may allow hydrogen ions to interact with sensory nerves in patients with NERD [75]. Dilated intercellular spaces may be useful in the objective diagnosis of NERD though there is some uncertainty left concerning their functional role [50, 76, 77]. There are also concerns regarding the specificity of dilated intercellular spaces as they are also found in association with psychological stress in animal models [78]. There is evidence that the dilated intercellular spaces may return to normal following adequate acid suppressant therapy, but the quality of evidence for their reversal is poor and the statement on the restoration of dilated intercellular spaces with acid suppression did not achieve consensus.

55. Basal cell hyperplasia and papillary elongations are histological abnormalities in NERD. 89% agree. Grade of evidence = Low

56. Morphological and biochemical signs of inflammation are present in a subset of NERD patients. 92% agree. Grade of evidence = Low

57. Advanced endoscopic technologies should be used to guide biopsies for pathophysiological studies of NERD. 58% agree. Grade of evidence = N/A

58. The majority of NERD patients have abnormalities on biopsies from the squamous epithelium in the distal esophagus. 69% agree. Grade of evidence = Very low

Established histological changes of GERD, which include elongation of the rete papillae and basal cell hyperplasia [79], are frequently detected in NERD, and these are restored to normal appearances by acid-suppressing therapy [80]. However, these abnormalities are also found in patients without symptoms and they have limited accuracy for the diagnosis of NERD since there is poor agreement on these observations by pathologists and no clear criteria have been described for diagnosis or therapeutic response [50]. Moreover, inflammatory cells are rarely seen in NERD [49].

It is anticipated that further progress in this field will follow the combined use of novel endoscopic techniques (such as high magnification and narrow band imaging) with targeted biopsies [81].

59. Disease entities distinct from NERD are detected by specific histomorphological abnormalities. 89% agree. Grade of evidence = Moderate

This assertion was widely accepted. Eosinophilic esophagitis, for example, may be clinically and endoscopically indistinct from NERD, yet it has characteristic his-

tological features [82]. Candidiasis and suspected viral or bacterial infections or patients with Crohn's disease are further reasons to biopsy to make a diagnosis or to differentiate from typical reflux disease.

60. *Transient lower esophageal sphincter relaxations are the principal mechanism underlying reflux events in NERD. 92% agree. Grade of evidence = Moderate*

61. *The mechanism of transient lower esophageal sphincter relaxation is similar in NERD and in healthy subjects. 97% agree. Grade of evidence = Low*

62. *Hiatal hernia is a not a major factor in the pathogenesis of NERD. 84% agree. Grade of evidence = Low*

Transient lower esophageal relaxation is the underlying mechanism that permits the reflux of gastric contents into the distal esophagus; this mechanism is probably common to both ERD and NERD, although there is surprisingly little published research in this area [83].

Whilst hiatus hernia is a recognized risk factor for the development of esophagitis, there have been few studies that have evaluated the role of hiatus hernia in the pathogenesis of NERD specifically. One recent study suggested that a small (<3 cm) hiatus hernia may contribute to the development of NERD, whereas an axial length of >3 cm was associated with a more severe disease [84], and in another study of patients with NERD and ERD hiatus hernia was found in 44 and 56%, respectively (not significantly different) [71].

Diagnosis and Treatment

63. *Following self- or pharmacist-advised care the vast majority of patients with reflux symptoms are treated by a family physician without investigation. 100% agree. Grade of evidence = Moderate*

64. *A structured assessment of symptom response by family physicians would facilitate management. 84% agree. Grade of evidence = Low*

Given the widespread public awareness of reflux disease and its management, most patients either treat themselves empirically with acid-suppressive medication or do so following advice provided by pharmacists. A personal assessment of symptoms by either patient and or physician is relatively inaccurate unless supported by the use of a valid symptom assessment tool [85]; the most effective method is by use of a patient completed questionnaire [86].

65. *A complete symptom response to antisecretory therapy provides moderate assurance that the symptoms are acid-related. 97% agree. Grade of evidence = Moderate*

66. *In the assessment of therapeutic efficacy, a standard dose course of empiric PPI therapy should be evaluated at 2–4 weeks, but some patients may take up to 12 weeks to respond. 100% agree. Grade of evidence = High*

67. *The persistence of reflux symptoms with adequate antisecretory therapy for greater than 12 weeks requires further assessment. 97% agree. Grade of evidence = Moderate*

The majority of patients who experience symptom relief with acid-suppressive medication likely suffer from GERD, but the identification of erosive disease requires endoscopy, and it is well established that symptom intensity and the degree of endoscopic damage noted correlate poorly [87]. Notwithstanding the placebo effect, almost all participants were of the opinion that a complete abolition of symptoms with acid-suppressing therapy provided evidence that the symptoms were indeed acid-related. For reasons that are unclear, and that may relate to individual differences in healing rates or variable visceral sensitivity, a group of patients do exhibit a delayed response to acid suppression, with symptom persistence for up to 12 weeks [17]. In those patients who have been fully compliant in terms of medication and fail to achieve symptom relief at 12 weeks of further investigation, in particular endoscopy, was considered warranted by almost all participants because of the need to consider alternate diagnoses.

68. *To establish a diagnosis of NERD, upper gastrointestinal endoscopy is required. 100% agree. Grade of evidence = N/A*

69. *The presence of alarm symptoms requires further investigation. 100% agree. Grade of evidence = Low*

70. *Routine random biopsy is currently not recommended for the diagnosis of NERD. 92% agree. Grade of evidence = Low*

71. *Additional diagnostic information is provided by ambulatory 24-hour intraesophageal pH-metry and impedance measurement with symptom correlation. 97% agree. Grade of evidence = Moderate*

By definition, the diagnosis of NERD depends on the exclusion of erosive disease by endoscopy. There was a unanimous recommendation for prompt endoscopy in a patient who presents with alarm symptoms, such as weight loss or progressive dysphagia. Such recommendations have become embedded in guidelines issued by

many national societies around the world [2], though objective evidence that prompt endoscopy for persistent or alarm symptoms improves clinical outcome is lacking. Biopsies of the distal esophagus at the time of endoscopy are not usually necessary if no visible abnormality is detected, they but can be useful to exclude specific diagnosis such as eosinophilic esophagitis [82]. In the future, biopsy may become routine if dilated intercellular spaces or other microscopic changes described in the section on pathobiological mechanisms above do become accepted criteria of NERD.

If the endoscopy is normal, empirical PPI treatment can be used to confirm that symptoms are acid-related and therefore that the likely diagnosis is NERD. If an adequate response is not observed by 8–12 weeks, and in the absence of other pharmacological agents (calcium channel blockers, alcohol) or non-compliance that might mitigate the efficacy of treatment, prompt re-evaluation of the underlying diagnosis is necessary. Measuring acid reflux by use of 24-hour pH-metry and/or impedance measurement will provide useful information, especially when abnormal acid exposure correlates with symptoms. Such studies are however complex to administer and interpret, and their routine use in clinical management inadvisable and impracticable unless a specialized center is available. Although such physiological investigations provide valuable information to better understand and manage NERD, it was felt by many at the meeting that the long-established criteria for abnormality in 24-hour pH studies [88] show relatively poor discrimination and should be re-evaluated. Although rare, consideration should also be given to the presence of covert intrinsic esophageal motility abnormalities (achalasia) or systemic disease such as scleroderma that might present with esophageal pain unrelated to acid reflux.

72. *The success of PPI therapy for symptom relief in NERD is generally lower than in patients with ERD. 92% agree. Grade of evidence = Moderate*

73. *Standard-dose PPI therapy should be started on a once-a-day basis. 97% agree. Grade of evidence = High*

74. *In patients with NERD who fail to achieve symptom response the physician should ensure treatment compliance and appropriate timing of PPI dose. 100% agree. Grade of evidence = Moderate*

75. *It is not established whether doubling the dose of a PPI will provide an incremental benefit on NERD symptoms. 97% agree. Grade of evidence = High*

76. *Failure to respond to twice daily PPI therapy renders the diagnosis of NERD unlikely and the need for continued*

PPI therapy should be re-evaluated. 92% agree. Grade of evidence = Moderate

77. *It is reasonable in patients who are PPI non-responsive to consider objective evaluation of gastroesophageal reflux. 92% agree. Grade of evidence = Low*

There was widespread support for the statement that the response rates to PPI therapy are lower in randomized trials of NERD patients compared with ERD patients [89]. It is therefore assumed that NERD patients respond less well to therapy than ERD patients, although it may be that the group designated as having NERD may include other patients with an as yet uncharacterized disease process, or with functional heartburn who should not now be included in NERD studies [8]. Nevertheless, PPI therapy is still the most effective therapy for NERD [89]. Initial treatment should comprise a standard once-daily dose 30 min before breakfast. For patients with NERD who fail to respond after 4 weeks, increasing the dose of PPI to twice daily is a common practice, but there is little objective evidence that this approach provides additional symptom relief. In general, the current standard of practice is to continue treatment with a once daily or twice daily PPI for up to 12 weeks. Patients who fail to respond to this regime are considered unlikely to have NERD and the continued use of PPI therapy in these patients should be reconsidered since there is no evidence to support the idea that increased therapy beyond 12 weeks confers any symptomatic benefit. Similarly, the persistence of symptoms at 12 weeks in a patient who is fully medication-compliant should prompt an objective assessment of gastroesophageal reflux [90].

78. *PPI therapy for NERD may be augmented with antacids or alginates in patients with incomplete symptom control. 67% agree. Grade of evidence = Low*

79. *The combination of continuous H₂RAs and PPIs in the treatment of NERD is of little clinical value. 86% agree. Grade of evidence = Moderate*

80. *In the evaluation of treatment of patients with NERD, a broad assessment of symptoms and QoL provides valuable indices of efficacy. 95% agree. Grade of evidence = Low*

81. *On-demand maintenance therapy is adequate for symptom control in a subset of patients with NERD. 95% agree. Grade of evidence = High*

82. *Continuous maintenance therapy is required for symptom control in a subset of patients with NERD. 97% agree. Grade of evidence = High*

83. *In patients who have had a good response to initial therapy, it is reasonable to stop therapy. 95% agree. Grade of evidence = High*

The group was unable to achieve consensus on whether supplementation of PPIs with antacids or alginates in patients with incomplete symptom relief was of benefit. Little objective evidence was available to either support or refute the point, and in the absence of any marked adverse effects for these drugs, it might be considered that such supplementation could be of benefit to individual patients.

The consideration of the addition of an H₂RA to a PPI in NERD 'non-responders' in the expectation of increased efficacy is not supported by any robust evidence. There may be an initial symptom response but this soon wears off due to tachyphylaxis to H₂RAs [91].

The exact delineation of an individual's response to treatment is important, since symptoms are the dominant feature of NERD. Validated tools are now available to measure a broad range of complaints in NERD, including QoL changes [85]. The use of such tools was considered key in defining the effectiveness of therapy [92]. For patients with NERD who show a good response to acid suppression, daily therapy may not be always necessary and many patients may already have chosen to take their treatment on-demand or intermittently [93]. In such cases the patient should be encouraged to continue with what works, including a trial of stopping all therapy. The group did, however, accept that there existed a subset of NERD patients who require continuous therapy to prevent recurrence of symptoms.

84. *For patients who have a failed response to a PPI, further investigation is essential to document gastroesophageal reflux before antireflux surgery is considered. 97% agree. Grade of evidence = Low*

85. *In NERD patients being considered for antireflux surgery, it should be objectively established that symptoms are attributable to reflux. 100% agree. Grade of evidence = Low*

The group concurred that surgery (laparoscopic fundoplication) was an option in NERD that should only be considered in extreme circumstances and after serious deliberation, given the well-documented serious adverse events that may be associated with surgery and the recognized benign course of NERD [94]. NERD patients with either no response or a poor symptom response to a PPI are poor candidates for antireflux surgery and little benefit can be predicted. Surgery should therefore only

be considered as an option in an extremely small group of NERD patients who show an excellent response to acid suppression and in whom objective evidence of reflux is demonstrable on investigation. Indeed, it is considered mandatory to demonstrate the presence of acid reflux and that the symptoms are attributable to such reflux episodes prior to any consideration for surgery. Overall, the consensus was that the use of an invasive intervention with known additional symptomatic consequences (bloating, flatulence) as well as potential serious risks (visceral perforation, bleeding, sepsis) was worthy of consideration only in exceptional circumstances and if undertaken in centers of excellence.

Conclusions

NERD is characterized by acid-related upper gastrointestinal symptomatology and is a separate entity to functional heartburn which is a symptom complex unrelated to reflux of gastric contents and thus excluded from the NERD definition. NERD cannot be distinguished from erosive esophagitis on the basis of symptoms and diagnosis of NERD requires the presence of reflux symptoms in the absence of abnormality at endoscopy. Validated reflux symptom questionnaires are important to evaluate symptoms in clinical trials of NERD patients and are likely to be of value in the future of clinical management of the disease. The association between the symptoms and reflux episodes is of importance in evaluating the results of pH and impedance monitoring in NERD patients, especially in those who are poorly responsive to acid suppression. The majority of patients with reflux symptoms are effectively managed by empiric PPI therapy prescribed by their family physician without knowing whether they have erosive or non-erosive disease. It is not established as to whether increasing the dose of a PPI will provide an incremental benefit on NERD symptoms while additional medications such as antacids and H₂RAs confer only transient if any advantage. The pathophysiological basis of NERD remains to be determined and the identification of abnormalities such as loss of functional mucosal integrity or neural hypersensitivity will likely lead to the development of additional therapeutic strategies.

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