NERD: a new approach in managing reflux symptoms

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Clinical revolutions come and go but doctors have to deal with the constancy of their patients and their problems. The advent of the acid suppression drugs, particularly the proton pump inhibitors (PPIs), initiated a revolution in the management of upper gastrointestinal problems. This was particularly effective for the management of gastroesophageal reflux disease (GERD), with the promise of a near abolition of symptoms. Suppressing acid was the key. The truth, as so often is the case, has however, turned out to be more complex and a little different. The original relatively simple entity of heartburn and reflux disease has transformed into a complex arborisation of clinical problems that embraces systemic symptoms, major quality of life issues, laryngeal and pulmonary problems and even a neoplastic threat - Barrett's! Now, to add further woe to the plight of both physician and patient comes NERD (non-erosive reflux disease); an entity that cannot be identified by endoscopy, has substantial symptomatology and is in many instances an acid related disorder. NERD may be considered as the major subcategory of GERD, which has assumed an increasingly important role and is considered in some parts of the world to have reached epidemic proportions. NERD is probably increasing at least as fast as its ``parent'' GERD, although more precise data regarding the epidemiology of NERD are only now beginning to emerge. In order to address the current concepts regarding NERD diagnosis and management a consensus meeting that included primary care physicians and gastroenterologists was recently held. This text places the information from that meeting into a context of use to physicians who manage patients with NERD.

GERD is a common condition with a prevalence of 20% or more in Western countries and is rising elsewhere. Overall, as many as 2% of the population are prescribed long-term acid suppression therapy and in one study more than 14% of people over 65 years were on PPIs. Despite this, the majority of those on long-term PPIs in primary care report moderate to severe ongoing symptoms and, if adherence is any measure of the success of these drugs, even early studies indicated that this was very patchy. Clinicians are coming to terms with the fact that there is no straight answer to dealing with the problems of symptom persistence which are more complex than previously thought and that acid suppression, while extremely effective when prescribed for acid related diseases may be of only modest benefit in conditions such as functional heartburn.

Why is this? Probably, in part, because of our failure to understand the aetiology of GERD and to assume that it was essentially an acid-related problem. It has been known that 70% of patients with GERD have a normal endoscopy and it is becoming clearer that it is the patient in this category who is less likely to be responsive to acid suppression. The correlation between symptoms and findings on endoscopy is only moderate. There is no difference in the type and severity of symptoms in those with either normal or abnormal endoscopies, in fact, normal endoscopy is even more likely in those who do not consult but have symptoms. These patients have been described as having endoscopy negative reflux disease but the newer category of NERD has emerged in order to formalise the classification.

Despite the high prevalence of such non-erosive disease, relatively little is known of its underlying pathophysiology, hence there is no clear guide to clinical management. Generally, NERD can be 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 in support of this diagnosis may include responsiveness to acid suppression therapy, abnormal reflux monitoring or the identification of specific novel endoscopic findings. Although NERD patients have impairment of quality of life similar to those with erosive esophagitis, they have an unpredictable response to acid suppression. Symptom response rates are at least 10-30% less than reported in patients with erosive reflux disease receiving similar doses and brands of PPIs.
contrast to GERD as a whole, women predominate in NERD, and as a group they are younger by a decade. Only 10% of those with NERD are discovered to have erosive oesophagitis over time and it is very unlikely that NERD is a precursor or an early development to erosive reflux disease. The two conditions appear to be distinct. Patients with NERD are thought to comprise a heterogeneous group in which the two most important mechanisms are considered to be the reflux of acid and non-acid contents and esophageal mucosal hypersensitivity. The dominance of acidic reflux in the etiology of the symptoms of NERD is underlined by the widespread agreement among the Consensus meeting participants that if the symptoms of a patient do not respond to acid suppressive medication or cannot be proven to be associated with an esophageal acid exposure on pH testing, then the diagnosis of NERD is unlikely. 

Acid and pepsin play a role in the symptoms and abnormal acid exposure is not the sole mechanism. Results from esophageal pH testing in NERD patients indicate an abnormality in less than two thirds of patients. In those with normal results, there tends to be a positive correlation between symptoms and reflux events. This suggests that NERD patients may be hypersensitive to normal levels of acid exposure in the esophagus. Hypersensitivity is a common denominator in many functional disorders, particularly irritable bowel syndrome but also in non-gastrointestinal problems, such as fibromyalgia. Non-specific associations such as non-cardiac chest pain and hoarseness are likely to be more associated with NERD than with erosive reflux disease. These provide pointers to a wider, cerebro-somatic mechanism associated with NERD, embracing the concept of the endophenotype. 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 erosive reflux disease.

However, in the majority of patients, it is impossible to predict from symptoms whether or not erosions will be present at endoscopy. Though based on relatively few and, in many instances, inadequate studies, most evidence to date argues against progression from NERD to erosive disease. How do we tackle NERD? There are no clear answers – the majority of patients will certainly respond to acid suppression if accurately diagnosed as having NERD. In the group that is not responsive, it has been suggested that increased doses might prove effective and that a response might take up to 12 weeks. In those that do not respond, it is likely that the diagnosis may not be NERD but rather functional heartburn. An important decision is to avoid entrenched, persistent treatment with acid suppression drugs if these are proving ineffective. The answer probably lies in modulating causes of frequent reflux, protecting the mucosa or in ways of attenuating the sensitivity of the oesophagus. If NERD is seen to lie within the complex of functional problems, drug-based therapies are likely to be challenging and may need augmenting with psychological interventions.

The vast majority of patients with GERD are seen initially and treated by a primary care physician without consideration of investigation. The diagnosis of NERD is not possible without an endoscopy although it is predictable that the vast majority will have a normal result, especially if they are younger. A definitive diagnosis is only possible after pH testing. These strategies are not practical in the everyday clinical setting. Whether a more detailed history or a structured symptom assessment can delineate NERD is highly debatable. Furthermore, a good response to acid suppression provides moderate rather than definitive assurance that the symptoms are acid related and does not in itself distinguish between erosive reflux disease and NERD.

The diagnosis of NERD may not make the symptoms of reflux any easier to treat than in patients found to have erosive disease. However, as for much of the clinical NERD literature, many of the patients in prior publications regarding symptom response would now be considered to have functional heartburn, so that the old concept of reflux symptoms responding less well to acid suppression in NERD than in erosive GERD requires re-evaluation. The best initial treatment for NERD is a standard once daily PPI, emphasizing to the patient the importance of taking the drug 30 minutes before breakfast. Failure to respond suggests issues with compliance, and although it is a well established common practice to then double the dose of the PPI (which should be given twice daily) there exists little objective evidence available that this provides any additional symptom relief. The consensus of the meeting group was that patients who fail to respond to a twice daily PPI would be unlikely to have NERD and therefore continued PPI use should be reconsidered. Although it has become common practice in the last few years to add a histamine H2 receptor antagonist to PPI treatment in “non-responders”, there is little rigorous evidence that this is helpful in the treatment of NERD. For patients with NERD who respond to acid suppression, daily therapy is not absolutely necessary and on-demand maintenance therapy is a perfectly acceptable means of achieving control of symptoms in many patients in whom it works.

To a large extent, the patient with NERD, whether or not formally diagnosed has not received informed, quality driven management. Clinicians have tended to regard them as difficult – often considering them to be non-compliant. This perceived resistance to entrenched clinical regimens has served to sideline these sufferers and has hindered the exploration of new therapeudic avenues. The categorization of NERD as a specific entity provides the opportunity for a review...
of the care of these patients. There is, however, a need to continue to assess this condition in the anticipation that clinicians will take a better researched and informed line. The concept of NERD opens new doors.

Disclosures

Pali Hungin has received research funding and has acted as advisor to several pharmaceutical companies working in gastroenterology including Nycomed; Irvin Modlin has worked with Nycomed in the capacity of a consultant and speaker.

References