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doi: 10.3748/wjg.14.3123

World J Gastroenterol 2008 May 28; 14(20): 3123-3128
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

Strategy for treatment of nonerosive reflux disease in Asia

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Received: February 25, 2008 Revised: April 1, 2008
Accepted: April 8, 2008
Published online: May 28, 2008

Abstract

The paper is to review the clinical and pathophysiologic differences between of nonerosive reflux disease (NERD) and reflux esophagitis (RE), and to propose a treatment strategy for NERD, especially for patients in Asia. A Medline search was performed regarding the clinical and pathophysiologic differences between NERD and RE, and treatment of NERD and RE. The characteristics of NERD patients in Asia are as follows: (1) high proportion of female patients, (2) low frequency of hiatal hernia, (3) high frequency of *H pylori* infection, (4) severe glandular atrophy of the gastric mucosa, and (5) frequent resistance to proton pump inhibitor (PPI) therapy. In Asian NERD patients, exposure of the esophagus to acid is not increased, and esophageal motility is normal. These characteristics are similar to those of patients in Western countries. Our recommended first-choice treatment is administration of PPI in combination with a prokinetic agent. However, at present, because there is limited evidence regarding effective treatments for NERD, it is best to try several different treatment strategies to find the best treatment for each patient.

Key words: Nonerosive reflux disease; Asia; Treatment

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Hiyama T, Yoshihara M, Tanaka S, Haruma K, Chayama K. Strategy for treatment of nonerosive reflux disease in Asia. *World J Gastroenterol* 2008; 14(20): 3123-3128 Available from: URL: http://www.wjgnet.com/1007-9327/14/3123.asp DOI: http://dx.doi.org/10.3748/wjg.14.3123

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications[1]. GERD is more common in Western countries than in Asian countries, such as China, Korea, and Japan. Epidemiologic studies show a prevalence of GERD symptoms in Western countries ranging from 20% to 40%[2,3] and in Asian countries ranging from 5% to 17%[4]. The prevalence in Asian countries has increased gradually[4]. Esophagogastroduodenoscopy (EGD) is the gold standard for the diagnosis of erosive GERD [reflux esophagitis (RE)], and the Los Angeles (LA) classification of esophagitis is generally accepted as the best means for endoscopic assessment of GERD[5]. In Japan, the prevalence of RE (LA classification grades A, B, C, and D) is approximately 15%, and most of these cases are grade A or B[6]. The majority of GERD cases are cases of nonerosive reflux disease (NERD).

NERD was previously considered a mild/early type of RE that would progress to severe RE. However, it was reported that, regardless of therapy, only 2.7% of NERD patients develop RE after 3 years and only 3% of patients develop RE after 6 years[7]. A recent retrospective study of 2306 GERD patients found that these patients at least two separate upper endoscopic examinations during the 7-year (mean) follow-up period. Examinations revealed that 69% of the patients were unchanged, 21% were improved, and 11% became worse[8]. Another study[9] reported similar results. These studies suggest that NERD rarely progresses to RE over time. In addition, NERD is significantly more refractory to treatment than RE[3]. Therefore, it was recently suggested that the underlying mechanism of development of NERD is different from that of RE. Here we review the clinical and pathophysiologic differences between NERD and RE and propose a treatment strategy for NERD, especially for patients in Asia.

Table 1 Clinical characteristics of NERD and RE patients in Asia

	NERD	RE
Male/Female	0.59-1.65	1.18-7.13
Average age (yr)	45.2-57.5	49.0-59.7
Mean body mass index (kg/m^2)	22.1-23.1	21.7-24.2
Complication of hiatal hernia (%)	17.7-34.8	35.1-77.0
H pylori infection (%)	36.3-48.3	18.0-32.3
Glandular atrophy of the gastric mucosa (open-type) (%)	25.0-43.0	6.7-25.0
Efficacy of proton pump inhibitor (%)	29.5-64.0	55.4-90.3

METHODS

Studies on GERD were identified by computerized and manual searches of the available literature. The Medline search (1975-2007) was performed using the following medical subject headings: reflux disease and Asia. Papers published in English were considered.

CLINICAL AND ESOPHAGEAL MOTILITY CHARACTERISTICS OF NERD IN ASIA

Several researchers examined characteristics of NERD and RE patients in Asia[10-18]. The male/female ratios ranged from 0.59 to 1.65 in NERD patients. On the other hand, those of RE patients ranged from 1.18 to 7.13. A higher proportion of female patients was observed in NERD patients compared with RE patients. There were differences between NERD patients and RE patients in frequency of hiatal hernia, frequency of *H pylori* infection, grade of glandular atrophy of the gastric mucosa, and effect of proton pump inhibitor (PPI) therapy as well. Namely, compared with the RE patients, the characteristics of NERD patients in Asia are as follows: (1) higher proportion of female patients, (2) lower frequency of hiatal hernia, (3) higher frequency of *H pylori* infection, (4) severe glandular atrophy of the gastric mucosa, and (5) frequent resistance to PPI therapy (Table 1). In addition, Asian NERD patients are more frequently affected by functional dyspepsia, irritable bowel syndrome, and psychiatric diseases than RE patients[13]. These characteristics are similar to those of Western NERD patients. However, there are several other characteristics in Western NERD patients, such as younger age and less obese[3]. As the prevalence of *H pylori* infection in Asian populations has decreased to levels similar to those in Western populations, these additional characteristics may be observed in Asian patients in the near future.

With respect to esophageal motility, NERD patients have several characteristics that differ from those of RE patients. In NERD patients, the resting lower esophageal sphincter (LES) pressure is not decreased. In addition, exposure of the esophagus to acid is not increased, and esophageal motility is normal (Table 2)[19]. These characteristics are similar to those of patients in Western countries, although the grades of motility index abnormalities in Asian RE patients are lower than those in Western RE patients[20].

Table 2 Esophageal motility characteristics in NERD and RE patients in Asia

	NERD	RE
Resting LES pressure	Mildly increased	Moderately decreased
Reflux episodes/hour	Moderately increased	Moderately increased
Primary peristalsis	Normal	Moderately decreased
Secondary peristalsis	Mildly decreased	Moderately decreased
Acid clearance	Mildly delayed	Moderately delayed

LES: Lower esophageal sphincter.

It seems that there are differences in pathophysiology between Asian RE patients and Western RE patients, because the grades of motility index abnormalities are different between them. However, there seems no significant difference in pathophysiology between Asian NERD and Western NERD patients, because clinical and esophageal motility characteristics are considerably similar between them.

PATHOPHISIOLOGY OF NERD

The main pathophysiology of RE is excessive exposure of the esophagus to gastric acid. Approximately 90% of patients with RE can be cured with a PPI, which is the strongest type of gastric acid suppressor[3]. In contrast, only one-third of NERD patients can be cured with a PPI. Although the cause of NERD that is responsive to PPI may be excessive exposure of the esophagus to acid, PPI-resistant NERD may be associated with the factors described below.

Incomplete acid suppression

In some patients, even the highest approved dose of PPI cannot sufficiently suppress gastric acid secretion. In patients with insufficient gastric acid suppression, gastric juice may reflux, exposing the esophagus to acid. The time required for metabolism of PPI differs between patients possibly due to polymorphisms in the genes encoding metabolic enzymes, such as CYP2C19[21,22]. In patients with the rapid metabolic phenotype, administration of twice the approved dose of PPI and concomitant administration of PPI and H_2-receptor antagonist (H_2RA) may be more effective[23,24]. It has also been reported that administration of an aluminum- and magnesium-containing antacid may be effective for some NERD patients[25].

Esophageal hypersensitivity to acid

Some patients with severe RE do not have symptoms of acid regurgitation, even if severe esophageal acid exposure is confirmed[26]. However, many NERD patients have a normal level of esophageal acid exposure. Therefore, there appears to be significant esophageal hypersensitivity to acid exposure in PPI-resistant NERD patients, and symptoms may occur when gastric acid is refluxed[27]. Hyperosmotic foods, such as cake and chocolate, and alcoholic beverages may be the cause of this esophageal hypersensitivity[28]. Ingestion of such

foods and drinks may cause heartburn. It has been suggested that ingestion of hyperosmotic foods/drinks loosens the tight junctions between esophageal epithelial cells, and when gastric acid is refluxed, it easily intrudes between epithelial cells and stimulates the terminals of sensory nerves[26].

Esophageal hypersensitivity to esophageal wall distension

In NERD patients, heartburn symptoms are induced by distension of the esophageal wall by balloon dilatation or by pumping saline into the esophageal lumen[29]. These findings suggest the possibility that foods, air, and fluids that contain no acid may cause heartburn symptoms simply by distending of the esophageal wall.

Reflux of duodenal juice (bile and pancreatic juice)

PPI suppresses gastric acid excretion but has no effect on reflux itself. Therefore, in patients with duodenogastric reflux, duodenal juice (bile and pancreatic juice) may be refluxed into the esophagus. It is possible that the refluxed duodenal juice may affect the esophageal mucosa[30]. NERD patients frequently have functional dyspepsia[4], and significant duodenogastric reflux and delayed gastric emptying time in patients with functional dyspepsia have been reported[31,32]. These findings support the idea that reflux of duodenal juice into the esophagus causes NERD.

Esophageal motility abnormalities

It has been reported that NERD patients show normal resting LES pressure and primary contraction waves but significantly reduced frequency of secondary contraction waves[19,33]. This may be due to a reduced response to distension of the esophageal wall. Secondary contraction waves are stimulated by distension of the esophageal wall and act to discharge refluxed gastric acid and air into the stomach. Heartburn symptoms may be associated with reduced motility function in the esophageal wall.

Sustained esophageal contraction

Sustained contraction of the longitudinal muscles of the esophagus causes heartburn, and prolonged contraction may lead to chest pain. This phenomenon is called sustained esophageal contraction (SEC) and is identified by intraluminal ultrasonography[34,35]. SEC occurs just before the onset of heartburn symptoms. There are two types of SEC: SEC with or without subsequent acid reflux. Because patients with the latter type also have heartburn symptoms, the association of SEC with NERD is of great interest.

Psychological factors

NERD patients frequently have mental disorders[13]. Psychological factors are associated with response to treatment as well as symptoms[36]. A high level of anxiety is predictive for the nonresponse to acid suppression therapy.

Eosinophilic esophagitis

Eosinophilic esophagitits affects both children and adults and is characterized by symptoms of GERD and dense esophageal eosinophilia, both of which are unresponsive to PPI[37,38]. This disease is caused by food allergies or by aeroallergens. Effective treatment include systemic/topical corticosteroids, or specific food elimination. Esophageal stricture is a potential complication, and the natural history of the disease is still unknown. Eosinophilic esophagitis may be diagnosed as PPI-resistant NERD, but should be excluded from the diagnosis of NERD.

TREATMENT STRATEGY FOR NERD IN ASIA

At present, PPI-based step-down treatment is recommended for GERD patients[39,40]. In a meta-analysis, the relative risks of PPI and H_2RA treatment for NERD compared with placebo were 0.69 (95% confidence interval, 0.62-0.78) and 0.84 (0.74-0.95), respectively, indicating that PPI is a more effective treatment than H_2RA[41]. PPI treatment can eliminate NERD symptoms faster than H_2RA treatment. In addition, PPI treatment has been reported to be more cost-effective than other treatment[42].

Prokinetics such as mosapride, itopride, metclopramide, and domperidone are also effective for treatment of NERD[43-45]. Prokinetics are thought to work by reducing reflux of duodenal juice into the esophagus[31] and speeding absorption of PPI. In addition, mosapride improves esophageal motility, whereas metclopramide and domperidone do not have this ability[46]. Mosapride shortens bolus transit time in the esophagus, reduces the duration of the longest reflux episode and reflux fraction time, and enhances the contraction strength in the lower esophagus.

Reflux of stomach contents is related to transient LES relaxation (TLESR) in NERD patients[47]. Therefore, control of TLESR is another important point for NERD treatment. 5-HT_3, cholecystokinin (CCK)-A, and gamma-aminobutyric acid (GABA) receptors influence TLESR[48-50]. 5-HT_3 receptor antagonist, CCK-A receptor antagonist, and GABA receptor agonist reduce the frequency of TLESR. Mosapride is a selective 5-HT_4 receptor agonist, and the metabolite acts as a 5-HT_3 receptor antagonist[51,52]. Therefore, mosapride reduces the frequency of TLESR, leading to reduced gastric acid reflux in NERD patients.

Some NERD cases are refractory to PPI and/or prokinetics. In these patients, psychological factors may be associated with symptoms. In these patients, administration of an antidepressant and/or minor tranquilizer should be considered. However, evidence for the benefits of these agents in treatment of NERD is weak[53], and further studies are needed to clarify the effects of such medications on NERD.

For NERD patients with infrequent symptoms of heartburn, on-demand therapy with PPI (and/or prokinetics) is proposed as the best treatment option[54,55]. Additional studies of the effectiveness of this treatment regimen are needed.

Here we propose a new strategy for treatment of NERD in Asia based on the basic idea of step-down

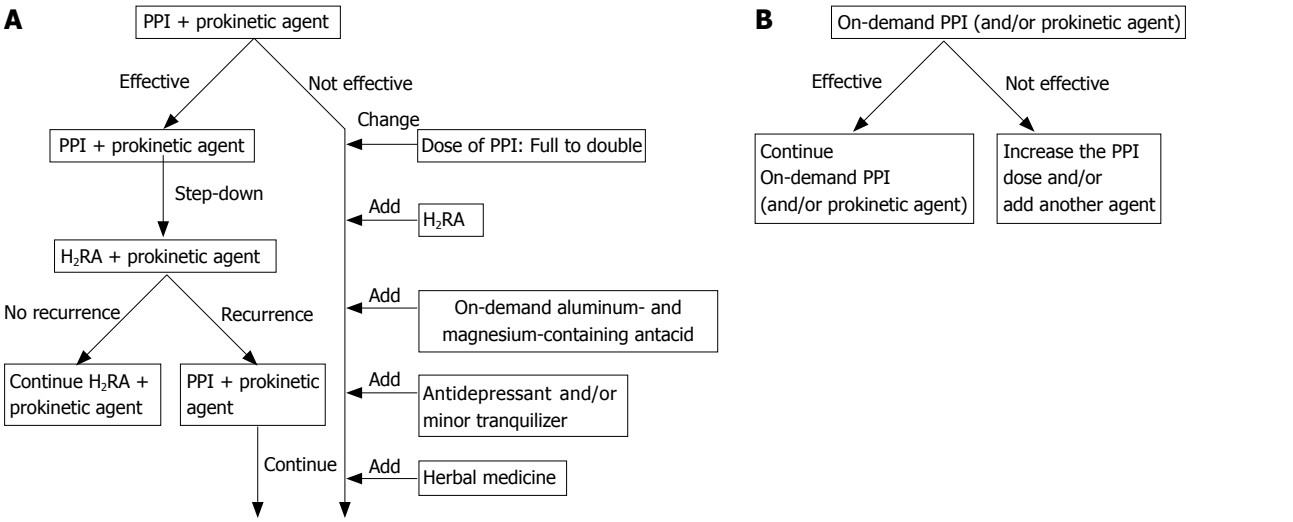

Figure 1 Proposed treatment strategy for NERD patients in Asia. **A**: Patients with moderate or severe symptoms; **B**: Patients with infrequent symptoms.

therapy (Figure 1). The recommended first-choice treatment is administration of PPI in combination with a prokinetic agent such as mosapride. PPI can cure only one-third of NERD patients, a prokinetic agent in conjunction with the PPI can increase the efficacy. NERD is frequently associated with functional dyspepsia that can be treated with prokinetic agents. In addition, because the quality of life of NERD patients is quite low, NERD patients need quicker and more effective treatment options[56]. If this treatment is not effective, twice the recommended dose of PPI or combined treatment with PPI and an H_2RA is recommended. PPI together with on-demand aluminum- and magnesium-containing antacid might be effective. If these treatments are not effective, administration of an antidepressant or minor tranquilizer should be considered. Herbal medicines such as rikkunshito may provide relief for some patients[57], and are often administered especially in Asian countries.

For patients with infrequent symptoms, on-demand treatment with PPI and/or a prokinetic agent is recommended. However, there is not sufficient evidence for a best treatment for NERD. Further studies are needed to clarify the efficacy of treatment. Large-scale, double-blind, randomized controlled trials of PPI *vs* PPI with a prokinetic agent are also needed to clarify the benefit of the prokinetic agent.

Further trials are needed to establish the strategy for treatment of NERD. At present, because there is limited evidence regarding effective treatments for the disease, it is best to try several different treatment strategies to find the best treatment for each patient.

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