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# Non-Erosive Reflux Disease: Improving Diagnosis and Treatment

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**Learning Objectives**

1. Understand the different subtypes of gastroesophageal reflux disease (GERD)
2. Describe the typical symptoms of GERD
3. Incorporate current best practices for diagnosing and managing non-erosive reflux disease (NERD)
4. Understand recent developments in the treatment of NERD

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## Definition and Classification of GERD

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal disorders for which primary care providers are consulted. The current definition of GERD is "*the condition in which the reflux of gastric contents into the esophagus results in symptoms and/or complications*".[1] This makes the important point that patients with GERD have symptoms with or without pathological damage to the esophagus.

The two main forms of GERD are erosive esophagitis (EE - also referred to as erosive GERD) and non-erosive reflux disease (NERD). Patients with EE have visible mucosal breaks (erosions) in the esophagus. Patients with NERD can have symptoms that are as severe – or worse – than those in EE[2] but have a normal-appearing esophagus at endoscopy. NERD is the more prevalent form of GERD – constituting about 70% of cases. Among patients with symptoms of GERD who have not had endoscopy, the term "symptomatic GERD" (sGERD) is sometimes used.

## The (Limited) Role of Endoscopy

NERD and EE can only be distinguished by endoscopy. However, in patients with typical symptoms of GERD, endoscopy is not required for initial diagnosis. Although endoscopy can distinguish whether a patient with GERD has EE or NERD, this does not influence initial management, which is discussed further below. Endoscopy is, however, recommended for patients with atypical or alarm symptoms and for patients whose symptoms do not respond to standard treatment.[1] In patients with EE, endoscopy can establish the severity of the condition and assess for possible complications such as stricture and Barrett's esophagus. Endoscopy also has a role in diagnosing esophageal conditions other than GERD (*e.g.*, eosinophilic esophagitis).

## Pathophysiology of GERD Explains Its Main Symptoms

The main symptoms of GERD are heartburn and regurgitation. Heartburn is a burning discomfort that typically starts in the lower chest and radiates upwards behind the sternum. It is typically worse after eating, after vigorous exercise, or on stooping or lying flat. Regurgitation is the effortless movement of fluid from the stomach up into the esophagus – or even into the throat.

The principal pathophysiological abnormality in GERD is dysfunction of the lower esophageal sphincter (LES). The LES, which separates the esophagus from the stomach, is normally closed and only relaxes briefly in response to swallowing or belching. However, in patients with GERD, these transient LES relaxations are excessive and allow for acidic gastric contents to reflux into the esophagus – thereby inducing the typical symptoms of heartburn and regurgitation.

## Making the Diagnosis of NERD

Although a normal endoscopy can distinguish NERD from EE, not all patients with symptoms suggestive of GERD and a normal endoscopy truly have NERD. Two other conditions – esophageal hypersensitivity and functional heartburn – may be confused with NERD.

In esophageal hypersensitivity, patients have normal, physiological episodes of gastroesophageal reflux (that we all experience from time to time – especially after meals). However, patients perceive these events as painful or uncomfortable. In functional heartburn, patients experience symptoms that are not associated with actual reflux events. Some patients with esophageal hypersensitivity may improve

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if given a medicine that reduces gastric acid secretion. Patients with functional heartburn are unlikely to respond to acid suppression.

Esophageal hypersensitivity and functional heartburn make the diagnosis of true NERD problematic. Technically, for a patient to have a firm diagnosis of NERD, there should be typical GERD symptoms, a normal upper endoscopy (while not taking a medicine that suppresses gastric acid secretion), demonstrated excessive reflux of acidic gastric contents into the esophagus, and a strong correlation between episodes of acid reflux and actual symptoms. The last two can only be obtained via intra-esophageal pH monitoring performed over 24 hours or longer. However, that investigation is not widely available and is not usually performed before making a presumptive diagnosis of NERD. This probably is not important for routine clinical practice; if a patient with presumed NERD responds favorably to treatment with an acid-suppressant, the diagnosis of NERD is more likely. For patients with little or no symptom improvement, the diagnosis is more likely to be functional heartburn[3] – and, for most, treatment with an acid-suppressant can be discontinued.

## The Role of Gastric Acid in GERD

Patients with GERD typically have normal levels of gastric acid secretion. GERD can therefore be considered as a condition in which stomach acid ends up in the wrong place. Gastric acid and pepsin (the other important secretory product of the stomach) are caustic to the esophageal mucosa. The esophagus is normally lined by stratified squamous epithelium with relatively wide intercellular spaces – unlike the stomach that is lined by a simple columnar epithelium with cells linked by tight junctions. The gastric mucosa also has a mucus-bicarbonate layer that further protects it from acid. The esophageal mucosa is much more vulnerable to gastric acid and pepsin than the stomach.

Despite gastric acid secretion being normal in most patients with GERD, we usually treat both EE and NERD with medicines that suppress gastric acid secretion. While it may seem more logical to instead address the dysfunction of the LES with a motility-modifying agent, we currently have no safe and reliable medicines that can correct the abnormal LES function or improve the clearance of refluxate from the esophagus. Therefore, gastric acid remains the best therapeutic target for the management of GERD. The different classes of acid-suppressing agents are discussed in greater detail below.

## Lifestyle Measures

The American College of Gastroenterology (ACG) clinical guideline on GERD management[1] discussed certain lifestyle measures that are often advised for patients with GERD; these are summarized in Table 1. Additional sensible measures such as curbing excessive alcohol consumption are obviously advisable from a general health perspective.

## Suppression of Gastric Acid Secretion for the Treatment of GERD

Patients with EE or NERD generally respond to treatment with medicines that reduce gastric acid secretion. These include H2-receptor antagonists, proton pump inhibitors (PPIs) and – most recently – potassium-competitive acid blockers (P-CABs).

The 2022 ACG clinical guideline[1] recommended that patients with typical symptoms of GERD – and no "alarm" symptoms (*e.g.*, dysphagia, unexplained weight loss, gastrointestinal bleeding) should be given an empiric 8-week course of a PPI. Since that guideline was published, the Food and Drug Administration (FDA) also approved the P-CAB vonoprazan for the treatment of EE or NERD in adults. While EE will not be further considered here, prescribers now have an additional option to consider for their patients with NERD. It is, therefore, important to compare and contrast the PPIs and P-CABs and understand the differences between these two drug classes.

**Table 1. Lifestyle measures recommended for patients with GERD**

| | Strength of recommendation | Level of evidence |
|---|---|---|
| Weight loss if overweight / obese | STRONG | MODERATE |
| Avoid eating within 2-3 hours of bedtime | CONDITIONAL | LOW |
| Avoid tobacco products | CONDITIONAL | LOW |
| Avoid trigger foods | CONDITIONAL | LOW |
| Elevate head of bed | CONDITIONAL | LOW |

Adapted from reference 1

**Table 2. Comparison of P-CABs and PPIs**

| P-CABs | PPIs |
|---|---|
| Act directly on the proton pumps in parietal cells | Pro-drugs that require to be converted in parietal cells to their sulfenamide (active) form |
| Bind competitively and non-covalently to the $K^+$-binding site of $H^+/K^+$-ATPase | Sulfenamide binds covalently $H^+/K^+$-ATPase |
| Binding is reversible | Binding is largely irreversible |
| Acid-stable so do not require enteric coating | Acid-labile so require enteric coating and delayed-release mechanism* |
| Do not require to be taken before food | Most should be taken 30 – 60 minutes before food for maximum effect** |
| Maximal effect on acid secretion is achieved within 1 to 2 days of once-daily dosing | Maximal pharmacodynamic effect may take up to 5 days of once-daily dosing |
| Elimination half-life of 7 – 8 hours | Elimination half-life of 1 – 2 hours |

Adapted from references 4-6.

* The exception to this is immediate-release omeprazole with sodium bicarbonate.

** The exceptions to this are dexlansoprazole and immediate-release omeprazole with sodium bicarbonate.

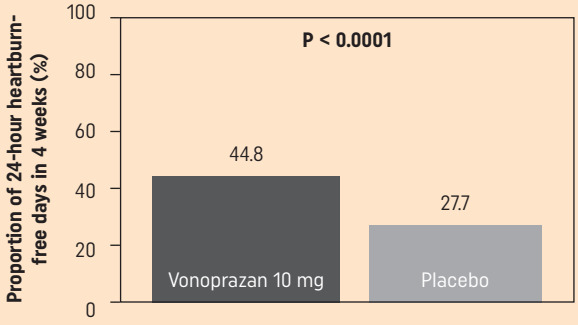
**Table 3. Comparison of the effects of the P-CAB vonoprazan and the PPI lansoprazole on gastric acid secretion in healthy subjects**

| | Day 1 | | Day 7 | |
|---|---|---|---|---|
| | Vonoprazan 20 mg | Lansoprazole 30 mg | Vonoprazan 20 mg | Lansoprazole 30 mg |
| Mean intragastric pH over 24 hours | 4.6 | 2.8 | 5.9 | 3.8 |
| Hours per day with intragastric pH > 4 | 15.6 | 5.4 | 21.1 | 10.2 |

Adapted from reference 7.

*P* < 0.0001 for all comparisons of vonoprazan and lansoprazole.

**Figure 1. Comparison of vonoprazan and placebo in adult patients with NERD**




**Proportions of 24-hour heartburn-free days on vonoprazan 10 mg or placebo once-daily over 4 weeks of double-blinded treatment.**

Adapted from reference 10.

PPIs have been available since the early 1990s. They are safe and effective for most patients with GERD although they do not control all patients' symptoms completely. PPIs are pro-drugs; they are chemically converted in parietal cells to their active form, which is termed a sulfenamide. The sulfenamide binds to proton pumps on parietal cells. Proton pumps (the enzyme $H^+/K^+$-ATPase) are responsible for the active secretion of hydrogen ions ($H^+$) into the stomach lumen in exchange for potassium ions ($K^+$). The sulfenamide binds covalently (and largely irreversibly) to the proton pump. PPIs are acid-labile and must be protected from gastric acid when taken by mouth. Different PPIs are given either as enteric-coated tablets or as capsules containing enteric-coated granules. The enteric coating dissolves in the proximal small bowel where the PPI is absorbed. Because of this, PPIs do not act immediately. In addition, it takes up to five days of once-daily dosing for a PPI to achieve its maximal effect in inhibiting gastric acid secretion. For optimal effect, most PPIs should be taken about 30 – 60 minutes before a meal.

By contrast, P-CABs are not pro-drugs and do not require chemical conversion in the parietal cell. P-CABs interfere with proton pump function differently than PPIs. P-CABs compete with canalicular $K^+$ for exchange with $H^+$ released by the pump in a non-covalent, reversible manner. P-CABs inhibit gastric acid secretion much faster than PPIs. They also inhibit acid secretion more potently than PPIs. Table 2 compares and contrasts PPIs and P-CABs from published information.[4-6]

A large study in healthy subjects in the US compared the effects of vonoprazan 20 mg once-daily with the PPI lansoprazole 30 mg once-daily when given for 7 days. Intragastric acidity was measured for 24 hours after the first and seventh doses of each drug.[7] The main findings of that study are summarized in Table 3. Vonoprazan started to act sooner than lansoprazole and had a greater effect on suppression of gastric acid secretion. As early as the first day of dosing, the mean pH in the stomach was significantly higher on vonoprazan than lansoprazole, and this difference was even greater on day 7. Similarly, vonoprazan kept the pH in the stomach above 4 for significantly longer than lansoprazole on the first and seventh days of dosing. When intragastric pH is above 4, stomach contents refluxing into the esophagus are much less acidic; they are also much less caustic as pepsin is not active at pH > 4.0. Vonoprazan has a longer elimination half-life than lansoprazole (7.9 hours *v.* 1.4 hours[7]). This may also contribute to its longer and greater effect on acid secretion.

## Efficacy of P-CABs in NERD

Most clinical trials of P-CABs in NERD have been conducted in Asia and have been reviewed elsewhere.[6] One study from South Korea compared the P-CAB tegoprazan (under development in the US but not currently approved) with placebo in NERD.[8] Tegoprazan 50 or 100 mg once-daily was superior to placebo for control of both heartburn and regurgitation. In a Japanese study, vonoprazan 10 mg once-daily was compared with placebo in NERD.[9] Over 4 weeks, vonoprazan produced a higher number of days free from heartburn than placebo and greater improvement in heartburn.

Vonoprazan was FDA-approved for the treatment of NERD in adults in July 2024. This approval was based on the results of a large placebo-controlled study.[10] Although vonoprazan was compared to placebo, this is the same standard by which some PPIs were given FDA approval for NERD.[11] Patients with NERD were randomized to vonoprazan 10 or 20 mg or placebo once-daily for an initial 4 weeks. Vonoprazan provided significantly greater control of heartburn than placebo as early as the first day of dosing. During the initial 4 weeks of the trial, vonoprazan 10 mg produced significantly more 24-hour heartburn-free days than placebo (Figure 1). Since the 20 mg dose

of vonoprazan was not more effective than the 10 mg dose, the approved dose of vonoprazan for NERD is 10 mg once-daily.

After 4 weeks of double-blinded treatment, patients who were started on vonoprazan continued on it for a further 20 weeks. Patients who received placebo for the first 4 weeks were switched to vonoprazan for the next 20 weeks. Patients who switched from placebo to vonoprazan had similar levels of symptom improvement as those who had initially received vonoprazan. While demonstrating the continued efficacy of vonoprazan among patients with NERD, not all such patients require continuous daily treatment. The current FDA approval for vonoprazan in NERD is for 4 weeks.

A large, US-based, placebo-controlled trial of the P-CAB tegoprazan for NERD has been completed. As of September 2024, its results were not publicly available.

## Communicating with Patients Regarding NERD

Patients with NERD can be reassured that, although they have troubling symptoms, these can usually be managed by sensible lifestyle modifications and medication. Furthermore, they can be told that they are not at increased risk of the serious complications of GERD, since these are essentially confined to those with EE. Not all patients with NERD require to take medication on a regular daily basis indefinitely; many can be adequately managed by taking their acid-suppressing medicine 'on-demand' or 'as needed'[12]. However, no medicine is currently FDA-approved for use in this manner.

## Conclusions

NERD is the more common form of GERD. It may be difficult to distinguish from esophageal hypersensitivity and functional heartburn. A positive symptom response to an acid-suppressing drug supports the diagnosis of NERD. Some PPIs and vonoprazan are FDA-approved for the treatment of NERD based on placebo-controlled trials. There are no trials comparing a PPI with a P-CAB in NERD. However, the more rapid onset of action of P-CABs and their ability to be taken regardless of mealtimes make them attractive options for managing patients with NERD.

## References


1. Katz P, Dunbar K B, Schnoll-Sussman F H et al. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol.* 2022;117:27–56
2. Joelson B, Johnsson F. Heartburn – the acid test. *Gut.* 1989;30:1523–1525
3. Aziz Q, Fass R, Gyawali C P, et al. Esophageal disorders. *Gastroenterology.* 2016; 150:1368–1379
4. Scarpignato C, Hunt R H. Towards extended acid suppression – the search continues. *Aliment Pharmacol Ther.* 2015;42:1027–1029
5. Abdel-Aziz Y, Metz D C, Howden C W. Potassium-competitive acid blockers for the treatment of acid-related disorders. *Aliment Pharmacol Ther.* 2021; 53:794–809
6. Kothadia J, Howden C W. Potassium-competitive acid blockers for the treatment of gastroesophageal reflux disease. *Foregut.* 2024;4:7–19
7. Laine L, Sharma P, Mulford D J, Hunt B, Leifke E, Smith N, Howden C W. Pharmacodynamics and pharmacokinetics of the potassium-competitive acid blocker vonoprazan and the proton pump inhibitor lansoprazole in US subjects. *Am J Gastroenterol.* 2022;117:1158–1161
8. Kim S H, Cho K B, Chun H J, et al. Randomised clinical trial: Comparison of tegoprazan and placebo in non-erosive reflux disease. *Aliment Pharmacol Ther.* 2021;54:402–411
9. Kinoshita Y, Sakurai Y, Takabayashi N, et al. Efficacy and safety of vonoprazan in patients with nonerosive gastroesophageal reflux disease: A randomized, placebo-controlled, phase 3 study. *Clin Trans Gastroenterol.* 2019;10:e00101
10. Laine L, Spechler S, Yadlapati R, et al. Vonoprazan is efficacious for treatment of heartburn in non-erosive reflux disease: A randomized trial. *Clin Gastroenterol Hepatol.* 2024;doi:10.1016/j.cgh.2024.05.004
11. Dean B D, Gano Jr A D, Knight K, Ofman J J, Fass R. Effectiveness in proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol.* 2004; 2:656–664
12. Khan Z, Alastal Y, Khan M A, Khan M S, Khalil B, Shrestha S, Kamal F, Nawras A, Howden C W. On demand therapy with proton pump inhibitors for maintenance treatment of non-erosive reflux disease or mild erosive esophagitis: A systematic review and meta-analysis. *Gastroenterology Research and Practice* 2018; article ID 6417526 (https://doi.org/10.1155/2018/6417526)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