Role of Gastric Acid Suppression Therapy in Erosive Esophagitis: From H2 Receptor Antagonists, Proton Pump Inhibitors, to Potassium-Competitive Acid Blockers

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ABSTRACT

Erosive esophagitis (EE) is an inflammation of the esophageal mucosa resulting from gastric and duodenal acid reflux, affecting approximately 55% of gastroesophageal reflux disease (GERD) patients in Indonesia. Effective acid suppression is essential for mucosal healing and symptomatic relief. Histamine-2 receptor antagonist (H2RA) was initially used for standard treatment for GERD, including EE, reducing gastric acid secretion by blocking H2 receptors. However, their efficacy is limited by inadequate acid suppression. Proton pump inhibitors (PPIs) became the mainstay therapy due to their stronger and longer-lasting acid suppression. Although PPIs have been proven to be quite effective, they have several limitations, including slow onset and inability to provide sustained acid suppression over a full 24-hour period. In recent years, Potassium-competitive acid blockers (PCAB) have become known as a category of drugs that effectively suppress gastric acid production, through a slightly different mechanism, and have advantages over PPIs, including faster onset and longer time of action. Both PPIs and PCABs can be used as therapy for patients with EE. PCABs are more recommended, especially in patients with severe grades of EE. H2RAs may still be considered in patients who have already received PPI therapy but continue to experience unresolved nocturnal acid symptoms.

***Keywords**: H2RA, proton pump inhibitor (PPI), Potassium-competitive acid blockers (PCAB), erosive esophagitis.*

INTRODUCTION

Erosive esophagitis (EE) is a condition characterized by inflammation of the esophageal mucosa, resulting from gastric and duodenal acid reflux.[1] EE impacts around 28% of individuals diagnosed with gastroesophageal reflux disease (GERD) globally. In Indonesia, the prevalence is notably higher, reaching about 55% of GERD patients.[2] EE manifests through a spectrum of symptoms, ranging from mild discomfort,

such as heartburn and regurgitation, to severe conditions like esophageal perforation. These symptoms greatly reduce quality of life and may elevate the likelihood of developing esophageal cancer.[3]

The primary approach to managing EE is through acid suppression therapy. Historically, histamine-2 receptor antagonists (H2RA), such as ranitidine, cimetidine, and famotidine, were the initial treatments utilized. These agents operate by blocking H2 receptors on parietal cells of the stomach, leading to a reduction in acid release. While H2RAs are beneficial for mild to moderate symptoms, they exhibit limitations, including a reduced capacity to suppress postprandial gastric acid secretion, rendering them less potent in managing reflux symptoms and promoting esophagitis healing.[4]

Subsequently, Proton Pump Inhibitors (PPI) became the recommended therapy for EE, as supported by various guidelines, including from The American College of Gastroenterology (ACG), The Asian Pacific Association of Gastroenterology (APAGE), and The Indonesian Society of Gastroenterology (*Perhimpunan Gastroenterologi Indonesia* / PGI).[5] PPIs, such as omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole, reduce gastric acid production more efficiently than H2RAs by permanently inhibiting the H^+/K^+ ATPase enzyme system in parietal cells of the stomach. However, PPIs have certain limitations, including slow onset and an inability to provide sustained acid suppression over a full 24-hour period.[6]

More recently, Potassium-competitive acid blockers (PCAB) emerged as an alternative to PPI. PCABs, such as Vonoprazan, Tegoprazan, and Fexuprazan, are active compounds that directly inhibit the gastric proton pump by competing with potassium ions, leading to rapid and sustained acid suppression. Unlike PPIs, PCABs do not require activation in a low-pH setting and can be taken independently of meal timing.[7]

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal Reflux Disease (GERD) is a condition in which the reflux of gastric and duodenal acid into the esophagus occurs. In Indonesia, the occurrence of GERD has been documented to reach up to 27.4%, significantly impacting patients' quality of life.[8,9] Several factors that can increase the risk of developing GERD include obesity, older age (>50 years), low socioeconomic status, alcohol and tobacco consumption, pregnancy, and the use of certain medications (such as anticholinergics, benzodiazepines, nonsteroidal anti-inflammatory drugs (NSAID), calcium channel blockers (CCB), and antidepressants.[10] Disorders such as esophageal dysmotility, lower esophageal sphincter (LES) dysfunction, transient LES relaxation, and delayed gastric emptying are considered fundamental mechanisms and may serve as primary causes of GERD.[11]

The majority of GERD patients can be classified into one of three categories: nonerosive reflux disease (NERD), erosive esophagitis (EE), and Barrett's esophagus (BE). The two primary GERD phenotypes—NERD and EE—exhibit distinct pathophysiological and clinical characteristics, and notably, they vary in how they respond to antireflux therapy.[12]

EROSIVE ESOPHAGITIS

Erosive esophagitis (EE) involves the erosion of the esophageal mucosa. Chronic exposure to gastric and duodenal acid leads to scar tissue formation, resulting in esophageal strictures. In prolonged cases, histopathological changes may occur, transforming the esophageal mucosa into metaplastic columnar epithelium, known as Barrett's esophagus, which increases the susceptibility of individuals to adenocarcinoma of the esophagus.[1]

The Los Angeles Classification is a system utilized to determine the extent of EE by categorizing mucosal break into four distinct levels: A, B, C, and D. Grade A is characterized by the presence of one or more mucosal lesions measuring no more than 5 mm, without reaching between the tops of two mucosal folds. Grade B is distinguished by mucosal lesions exceeding 5 mm in length, yet not extending between the tops of two mucosal folds. In contrast, grade C is identified by mucosal lesions that span across the tops of two or more mucosal folds

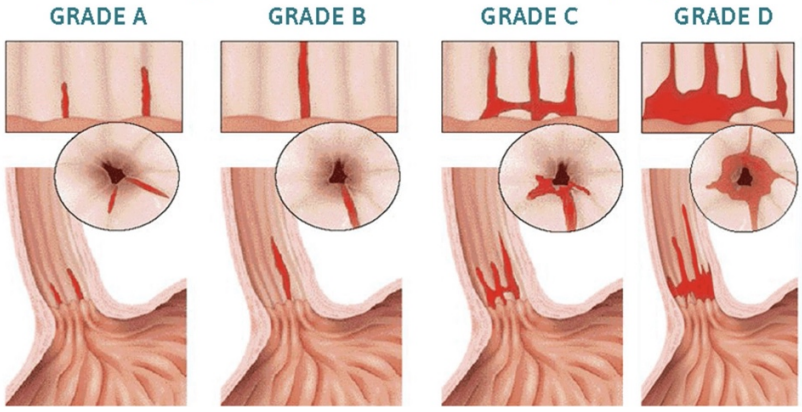

Figure 1. Los Angeles Classification of EE[13]

while affecting less than 75% of the esophageal perimeter. Lastly, grade D represents the most severe stage, where mucosal lesions involve at least 75% of the esophageal perimeter.[13]

EE is frequently encountered in primary healthcare settings and poses a significant health burden as a result of its detrimental effects on overall well-being. The prevalence of EE varies by region, affecting 10–20% of the population in Western countries and around 5% in Asian populations. In Indonesia, 55.4% of GERD patients have been found to experience EE, with 64.5% of these cases classified as Grade A based on the Los Angeles Classification.[14,15]

ETIOLOGY AND PATHOPHYSIOLOGY

Several key mechanisms play a role in exposing the esophagus to gastric and duodenal acids, primarily related to the inability of the distal esophagus to maintain its barrier function, leading to retrograde regurgitation. The development of EE and BE is not solely due to acid exposure causing chemical injury. The irritation triggers nuclear factor kappa-light-chain-enhancer of activated B cells and hypoxia-inducible factor-2 alpha, increasing inflammatory T-cell infiltration and pro-inflammatory cytokines, resulting in esophageal damage.[16] The following are key mechanisms underlying the reflux of gastric fluids into the esophagus[17,18]:

- Transient Lower Esophageal Sphincter Relaxation (TLESR): A decrease in resting pressure of the lower esophageal sphincter (LES) impairs its capacity to inhibit retrograde flow, allowing bile acids, gastric acid, and pepsin to reflux into the esophagus.
- Hiatal Hernia: This condition disrupts the anatomical alignment of the diaphragm and lower esophagus, weakening the sphincter's function. The hernial sac can serve as a holding chamber for gastric fluids, which may flow back into the esophagus while deglutition or while lying down.
- Increased Intra-abdominal Fat: Excess adipose tissue elevates intra-abdominal pressure, increasing the gastroesophageal pressure gradient and raising the occurrence of TLESR.
- Impaired Physiological Defense Mechanisms: Patients with esophageal peristaltic dysfunction and/or reduced saliva production may experience GERD symptoms. Normally, minor reflux episodes are cleared by peristalsis. Impaired acid clearance leads to prolonged mucosal exposure to gastric contents.
- Esophageal Mucosal Defense Mechanism Dysfunction: This defense comprises pre-epithelial, epithelial, and post-epithelial components. The pre-epithelial layer, consisting of water and bicarbonate from saliva and submucosal gland secretions, neutralizes refluxed acid. The epithelial component includes mechanical and chemical barriers like tight junctions, intracellular buffers, and membrane transporters. The post-epithelial layer's blood supply aids in mucosal regeneration following injury.
- Psychosomatic Factors: Chronic stress and anxiety affect the autonomic nervous system,

which regulates gastrointestinal motility and acid secretion. Stress increases sympathetic activity and decreases parasympathetic activity, leading to LES dysfunction and heightened acid production. Additionally, stress can alter pain perception, increasing visceral sensitivity and exacerbating GERD symptoms, thereby further diminishing patients' quality of life.

DIAGNOSIS

Diagnosis and classification of EE require confirmatory diagnostic testing, primarily through esophagogastroduodenoscopy (EGD).[19] Clinical manifestations of EE include common symptoms such as heartburn and regurgitation, as well as unusual presentations such as chronic cough, chest pain, asthma, dental erosion, dysphonia, and sore throat. Additionally, approximately 30% of patients with reflux esophagitis experience dysphagia, which may indicate complications such as esophageal stricture.[20]

Currently, the Indonesian national guidelines for GERD management recommend a symptom-based approach using the validated Gastroesophageal Reflux Disease Questionnaire (GERD-Q) (Table 1).[14] The GERD-Q is composed of six items assessing GERD symptoms experienced in the previous week, with four focusing on symptoms that are positive indicators for GERD diagnosis, including heartburn, regurgitation, sleep disturbances, and the use of over-the-counter medications. The remaining two items evaluate symptoms regarded as negative indicators of reflux, such as epigastric pain and nausea. Each item is answered based on the occurrence of these symptoms over the past week using a Likert-like rating system, ranging from 0 to 3 for positive indicators and from 3 to 0 for negative indicators.[21] A total score of 8 or above suggests a GERD diagnosis. Patients meeting this threshold should undergo a therapeutic trial with PPI therapy to assess treatment response. For those presenting with alarm symptoms or demonstrating a lack of response to empirical PPI therapy, EGD is required as the gold standard diagnostic modality. This procedure not only verifies the presence of esophagitis but also assesses the extent of mucosal damage according to the Los Angeles Classification.[14]

Siahaan et al. reported that individuals with a GERD-Q score of at least eight have a 2.6-fold higher likelihood of developing reflux esophagitis compared to those with a GERD-Q score below eight, with a p-value of 0.012.[22] Similarly, Simarmata et al.[23] discovered a strong correlation between the GERD-Q score and endoscopic findings of esophagitis with $r = 0.643$ and p value < 0.001.[23] Both studies suggest that the GERD-Q questionnaire could serve as a diagnostic modality for reflux esophagitis and has the potential to clinically differentiate severity levels. However, endoscopic examination continues to be the gold standard for confirming a GERD diagnosis associated with EE.

MANAGEMENT

The primary approach to managing EE is to address GERD, aiming for symptom relief and mucosal healing. There are five key therapeutic goals in GERD management: alleviating patient symptoms, promoting mucosal healing, preventing disease recurrence, improving patients' quality of life, and minimizing potential complications.[14]

Non-Pharmacological Management

Non-pharmacological interventions play a crucial role, particularly in weight management. GERD patients are advised to avoid consuming food at least three hours before bedtime and raise the upper part of the bed by 15–20 degrees to minimize the risk of acid reflux during sleep.[14] Additionally, certain lifestyle factors should be avoided, as they can trigger acid production, including alcohol ingestion, smoking, and specific foods such as caffeine, chocolate, carbonated drinks, spicy foods, and alcohol.[24]

Pharmacological Management

In most cases, pharmacological intervention is required to achieve optimal therapeutic outcomes. ACG, APAGE, and PGI recommend acid-suppressive agents as the primary treatment for EE, including PPI, with H2RA or PCABs as alternatives. Other medications such as baclofen, prokinetics, sucralfate, alginates, and

rebamipide may be considered as adjunctive therapy, depending on the patient's presenting symptoms.[25–27]

Histamine-2 Receptor Antagonists (H2RA)

Before the widespread use of PPIs, H2RA were the primary pharmacological therapy for GERD and EE. H2RA functions by competitively blocking histamine from attaching to H2 receptors on gastric parietal cells, resulting in decreased acid secretion. Unlike PPI and PCAB, which target the proton pump, H2RA works upstream in the acid production pathway, leading to moderate acid suppression.[28,29]

H2RA was initially effective in managing GERD symptoms and mild to moderate EE. However, their efficacy is limited in regulating postprandial acid production, and they are not as potent as PPIs in promoting mucosal healing in EE. Additionally, prolonged use of H2RA is linked with the development of tachyphylaxis, where their acid-suppressive effects diminish over time due to upregulation of histamine receptors.[30]

Despite their limitations, H2RA still holds a role in GERD management, especially in cases of mild reflux disease, as an adjunctive therapy for patients with breakthrough nocturnal acid secretion (nocturnal acid breakthrough). ACG, APAGE, and PGI continue to recommend the nighttime use of H2RA in patients with GERD who experience unresolved nocturnal symptoms. The administration of nighttime H2RA in patients with GERD has been shown to significantly reduce the percentage of time gastric pH remains below 4 during the supine period, compared to twice-daily PPI therapy alone.[25–27]

Proton Pump Inhibitors (PPIs)

The primary pharmacological management for GERD and EE is PPIs, which work by permanently blocking the H+/K+ ATPase proton pump in gastric parietal cells. These cells are essential for gastric acid production. At therapeutic concentrations, PPI accumulates in the proton-producing canaliculi of parietal cells before inhibiting the proton pump. This mechanism effectively suppresses acid production until new proton pumps are synthesized, requiring repeated PPI administration to maintain acid suppression. However, PPIs do not interfere with the underlying pathophysiology of mechanical reflux, nor do they reduce the frequency of reflux episodes.[31]

Various PPIs are available, including omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. Although they share a common mechanism of permanently blocking the H+/K+ ATPase proton pump, their pharmacokinetic and pharmacodynamic properties vary, affecting onset of action, bioavailability, and half-life.[32]

PPIs remain the first-line therapy for the management of EE, both during the healing and maintenance phases.[25–27]

PPIs are best administered 30–60 minutes before meals. In patients with EE, an 8–12 week course of PPI therapy is recommended to relieve symptoms and promote mucosal healing of the esophagus. However, in some cases, patients may continue to experience nocturnal symptoms. In such instances, the PPI dose may be increased to twice daily, or a nighttime H2RA may be added, as previously described.[26]

PPIs showed a significantly faster healing rate (12%/week) vs H2RAs (6%/week), and faster, more complete heartburn relief (11.5%/week) vs H2RAs (6.4%/week). PPIs are associated with a greater rate of “complete” symptom relief (usually assessed at 4 weeks) in patients with EE (70%–80%) compared with patients with so-called NERD, in which symptom relief approximates 50%–60%.[26]

No single PPI has been demonstrated to be significantly inferior in acid suppression for GERD and EE treatment. However, esomeprazole, the S-isomer of omeprazole, is reported to provide more potent acid suppression than other PPIs. Kalaitzakis et al. conducted a systematic review and found that daily administration of 40 mg of esomeprazole for eight weeks led to higher mucosal healing rates and symptom resolution in EE compared to 20 mg of omeprazole, 30 mg of lansoprazole, and 40 mg of pantoprazole.[32] Additionally, 20 mg of esomeprazole demonstrated greater effectiveness in maintaining mucosal recovery in EE in relation to 15 mg of lansoprazole or 20 mg of pantoprazole, although the variations were not

statistically meaningful.[32–34]

PPI therapy is typically initiated upon GERD diagnosis, often guided by the GERD-Q questionnaire. For EE patients, pharmacologic treatment is tailored to the extent of mucosal damage, classified by the Los Angeles classification. Mild cases (grades A and B) are managed with on-demand therapy until symptom resolution and mucosal healing are achieved. In contrast, severe esophagitis (grades C and D) requires up to six months of continuous PPI therapy. Patients who do not show a response to PPIs require further testing to exclude conditions like irritable bowel syndrome, delayed gastric emptying, achalasia, eosinophilic esophagitis, or psychological disorders.[14]

Potassium-Competitive Acid Blockers (PCABs)

PCABs are a newer group of acid suppression therapies that, similar to PPIs, act on the H+/K+ ATPase proton pump in gastric parietal cells. However, unlike PPIs, PCABs exert their effect by competitively inhibiting potassium ions (K+) from attaching to the proton pump, thus directly suppressing acid secretion. This ionic binding mechanism makes PCAB more stable in acidic environments, eliminating the requirement for enteric coating or the necessity of taking them 30 minutes before meals. Additionally, PCAB acts immediately upon administration, achieving peak plasma concentration faster than PPIs, which require activation in acidic conditions. PCAB also has an extended plasma half-life, leading to prolonged acid inhibition compared to PPIs. In vitro studies indicate that vonoprazan, a widely studied PCAB, is primarily metabolized by CYP3A4, making it effective across all CYP2C19 genotypes, a factor that influences PPI metabolism and efficacy.[35]

Currently, two primary PCABs, vonoprazan and tegoprazan, have been investigated in clinical studies. While multiple studies have compared PCABs and PPIs, there is still limited direct comparison between vonoprazan and tegoprazan, as both are relatively new agents.[36] These PCABs differ in selectivity and affinity for potassium receptors on the H+/K+ ATPase pump, leading to variations in half-life, onset of action, and serum gastrin levels.[37]

Despite being a novel therapy, tegoprazan has fewer large-scale clinical trials evaluating its efficacy and safety, whereas vonoprazan has been more extensively studied, demonstrating superior efficacy and safety compared to PPIs in a broader patient population.[38] The key differences between each class of acid suppression therapy are summarized in **Table 2**.

Table 2. Comparison of Characteristics and Potential Implications Between PPIs and PCABs[7]

Characteristic	PPI	PCAB
Prodrug activation	Prodrugs with a pKa ~4 Require conversion to the active form in an acidic environment, leading to a delayed onset of action.	Bind directly to the H^+/K^+-ATPase in parietal cells by competitively inhibiting potassium ions, enabling immediate acid suppression.
Plasma half-life	Short plasma half-life (1–2 hours) Limited duration of effect; requires synthesis of new proton pumps once drug levels decrease below the activation threshold.	Longer plasma half-life (e.g., Vonoprazan: 7.7 hours; Tegoprazan: 3.6–5.4 hours), providing prolonged acid suppression.
Acid stability	Acid-labile. Requires an enteric coating that is dependent on pH for protection and absorption.	Stable in acidic environments; does not require enteric coating.
Onset of action	Gradual onset of pharmacodynamic effect (stabilizes after 3–5 days). Limited efficacy in controlling intermittent or breakthrough symptoms, such as sporadic epigastric pain.	Faster onset of therapeutic effect.
Timing of administration	Must be taken 30–60 minutes before meals, potentially affecting patient adherence and therapeutic outcomes.	Can be administered independently of meal timing, enhancing convenience and adherence.
Duration of action	Duration of action is less than 24 hours. It may reduce effectiveness in treating certain acid-related disorders.	Provides a longer duration of action compared to PPIs.

Ashida et al. conducted two studies in 2015 and 2016, demonstrating that patients with erosive esophagitis (EE) experienced better mucosal healing when treated with Vonoprazan 20 mg once daily compared to Lansoprazole 30 mg once daily, especially after two weeks of treatment, and particularly in patients with severe EE (LA grade C and D).[39,40] In 2023, A study by Laine et al, Vonoprazan 20 mg once daily was associated with better gastric mucosal healing and slightly improvement of symptom relief—particularly in achieving heartburn-free status—than in the Lansoprazole 30 mg once daily, with the difference being more pronounced in patients with severe EE (LA grade C and D).[41] Similarly, the study by Xiao et al., conducted in 2020, reported that 20 mg of Vonoprazan resulted in better mucosal improvement compared to 30 mg of Lansoprazole after two weeks of treatment; however, the difference between the two groups was not statistically significant.[42]

Lee et al. compared Tegoprazan at doses of 50 mg and 100 mg with Esomeprazole 40 mg in patients with EE. After 4 weeks of treatment, the post-treatment analysis showed that Esomeprazole 40 mg was slightly more effective than both doses of Tegoprazan, although the difference was not statistically significant.[43] Similarly, Cho et al. (2022) compared Tegoprazan 25 mg with Lansoprazole 15 mg in EE patients and found that Lansoprazole showed slightly better early mucosal healing within the first 12 weeks of therapy, although the difference was again not statistically significant.[44]

Sakurai et al., in 2019, reported that Vonoprazan and Esomeprazole provided similar symptom improvement at 1, 2, and 4 weeks in the overall population of patients with GERD. However, among patients with EE, Vonoprazan demonstrated a slight advantage over Esomeprazole, although this difference was not statistically significant, likely due to the small sample size in the subgroup analysis.[45]

Various comparative studies have demonstrated that both PPIs and PCABs are similarly effective in the management of EE. While some studies suggest a potential advantage of PCABs, these differences are often not statistically significant. Some studies indicate comparable outcomes or even a slight superiority of PPIs.[39,42–44] However, studies that stratify patients by EE severity—mild (LA grades A and B) versus severe (LA grades C and D)—indicate that the benefits of PCABs appear more pronounced in patients with severe EE.[41,45] This may be attributed to the prolonged acid exposure time typically observed in severe EE, which makes the stronger acid-suppressive effect of PCABs more clinically relevant compared to PPIs.[46]

CONCLUSION

Both proton pump inhibitors and potassium-competitive acid blockers can be administered as therapy for patients with erosive esophagitis. PCABs are more strongly recommended for patients with severe grades of erosive esophagitis. Histamine-2 receptor antagonists (H2RA) may still be considered for patients who have been treated with PPIs but continue to experience unresolved nighttime symptoms.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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