

Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome

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One of the hallmarks of the mammalian stomach is its ability to secrete large quantities of concentrated (0.16 mol/L) hydrochloric acid (HCl).¹ Although it is generally assumed that gastric acid and the proteolytic enzyme pepsin are required to initiate digestion, achlorhydric individuals generally do not develop malabsorption unless small bowel bacterial overgrowth is present. It is thus likely that the ability of the stomach to secrete acid evolved primarily from a need to sustain a sterile intragastric milieu. Organisms that possessed the capacity to kill ingested bacteria and other microbes were able to avoid the development of enteric colonization, and thereby ensure both efficient absorption of nutrients and prevention of systemic infections.¹ Nevertheless, when present, gastric acid does play a significant role in protein hydrolysis and other aspects of the digestive process, and under various conditions, acid may play an etiologic role in producing various forms of discomfort and inciting esophageal and gastroduodenal mucosal injury.

The normal human stomach contains approximately 1 billion parietal cells that secrete hydrogen ions into the gastric lumen in response to various physiological stimuli. The generation of H⁺ ions is mediated by 3 pathways: neurocrine, paracrine, and endocrine (Figure 1). The principal neurocrine transmitter is acetylcholine, which is released by vagal postganglionic neurons and appears to stimulate H⁺ ion generation directly via a parietal cell muscarinic M₃ receptor. Histamine is the primary paracrine transmitter that binds to H₂-specific receptors on parietal cells. Adenylate cyclase is then activated, leading to an increase in adenosine 3',5'-cyclic monophosphate (cAMP) levels and subsequent generation of H⁺ ions. The secretion of gastrin from antral G cells comprises the endocrine pathway and stimulates H⁺ ion generation both directly and indirectly, the latter by stimulating histamine secretion from enterochromaffin-like (ECL) cells of the corpus and fundus. Interactions among neurocrine, paracrine, and endocrine pathways are coordinated to promote or inhibit H⁺ ion generation. Hista-

mine appears to represent the dominant route, because gastrin stimulates acid secretion principally by promoting histamine release from ECL cells.^{2,3} Thus, ECL cells are often referred to as "controller" cells in the process of gastric acid secretion.

A negative feedback loop governs both gastrin release and the return of acid secretion to basal level.^{1,4-6} This autoregulatory mechanism prevents postprandial acid hypersecretion. After ingestion of a meal, gastrin release stimulates secretion of gastric acid. The intraluminal pH begins to decrease, which stimulates release of somatostatin from antral D cells, possibly through the activation of calcitonin gene-related peptide (CGRP) neurons.^{5,7} Somatostatin then appears to act via a paracrine mechanism to inhibit further release of gastrin from G cells.⁸ Somatostatin produced by D cells in the gastric corpus and fundus may also directly inhibit acid secretion from parietal cells and may suppress histamine release from ECL cells (Figure 1).^{6,9} Other recent observations indicate that several other neurotransmitters, including vasoactive intestinal peptide (VIP), galanin, and pituitary adenylate cyclase-activating peptide, may play important roles in regulating gastric acid secretion, both directly and indirectly, under physiological conditions.¹⁰

Pathophysiology of Acid-Related Disorders

Gastroduodenal (Peptic) Ulcer

The treatment of duodenal ulcer (DU) has served as the basis (correctly or incorrectly) for the management of nearly all acid-related disorders. This supposition in all likelihood contributed to delays in the optimal management of other gastrointestinal (GI) disorders in which

Abbreviations used in this paper: DU, duodenal ulcer; ECL, enterochromaffin-like; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GU, gastric ulcer; NCCP, noncardiac chest pain; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

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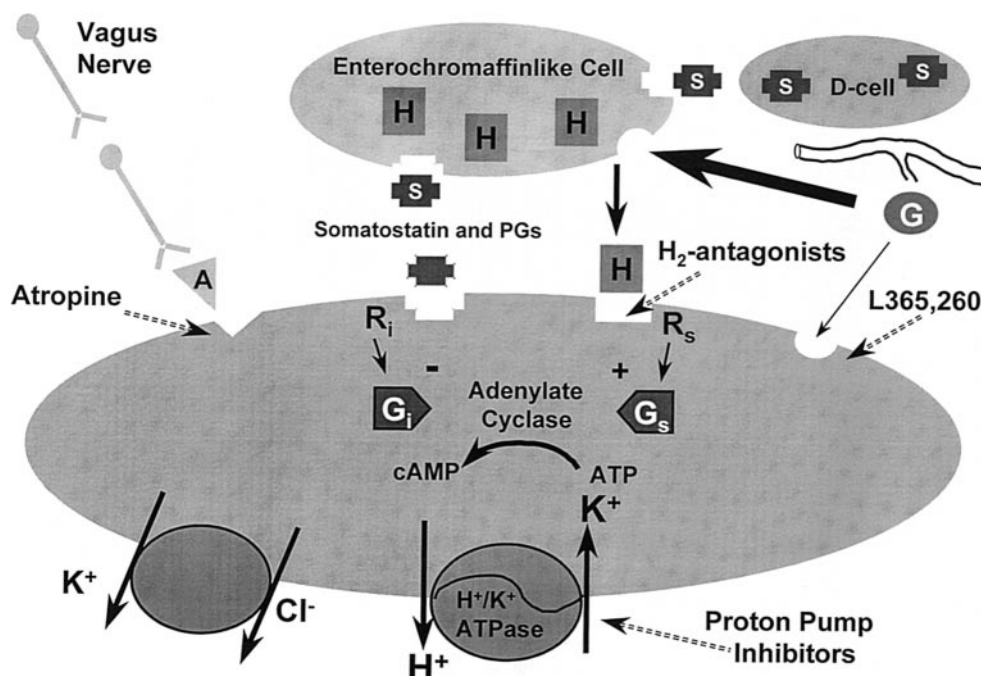


Figure 1. Schematic representation of the factors influencing gastric acid secretion by the parietal cell, depicting neurocrine (acetylcholine and other neurotransmitters from vagal efferent neurons), paracrine (somatostatin from D cells and histamine from gastric ECL cells), and endocrine (circulating gastrin) factors. Dashed arrows indicate potential sites of pharmacological inhibition of acid secretion, either via receptor antagonism or via inhibition of H^+,K^+ -ATPase. A, acetylcholine and other neurotransmitters; H, histamine; G, gastrin; L365,260, synthetic gastrin receptor antagonist; PG, prostaglandin; S, somatostatin.

acid plays an etiologic role in producing symptoms and causing mucosal injury, such as gastroesophageal reflux disease (GERD). Although patients with gastric ulcers (GUs) tend to have normal or reduced levels of acid secretion,¹ the average DU patient is an acid hypersecretor. When compared with age-matched controls, DU patients secrete ~70% more acid during the day (meal-stimulated) and about 150% more acid at night (basal secretion) (Figure 2).¹¹ Postprandial gastric acid secretion is regulated primarily by increases in gastrin expression, which is controlled by a negative feedback loop. Individuals infected with *Helicobacter pylori* have been shown to have a diminished number of somatostatin-secreting D

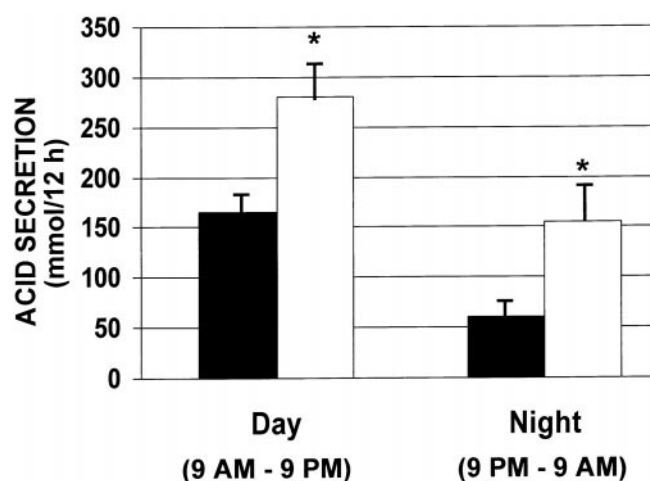


Figure 2. Gastric acid secretion during the day and night in patients with DU (n = 8) and in age-matched controls (n = 7). Acid secretion is expressed as the mean $\pm$ SE in millimoles per 12 hours. * $P < 0.05$. Data from Feldman et al.¹¹

cells, which decreases the magnitude of the response to luminal acidification.¹²⁻¹⁴ Thus, in patients with *H. pylori* infection limited to the antrum, the negative feedback inhibition of gastrin release is attenuated, resulting in higher postprandial gastrin levels and hypersecretion of acid.

Despite the existence of meal-induced hyperchlorhydria in DU patients, the presence of food in the stomach has a buffering effect that may protect the gastroduodenal mucosa from acid-induced injury. However, at night and during other prolonged periods of fasting, acid bathes the "bare" mucosa, and in DU patients, the increase in nocturnal acid secretion magnifies this effect. Duodenal bicarbonate secretion also appears to be impaired in patients with DU,¹⁵ as well as in those infected with *H. pylori*, making the mucosal exposure to acid even greater. These observations, as discussed below, form the rationale for single nocturnal dosing of H_2 -receptor antagonists in the treatment of DU, a mode of therapy that is at least as effective as multiple dosing regimens.

Clearly, factors other than acid and pepsin are involved in the pathogenesis of peptic ulcer disease (PUD), because only 30% of patients with DUs and very few patients with GUs are hyperchlorhydric.¹ The balance between aggressive factors that act to injure the gastroduodenal mucosa and defensive factors that normally protect against corrosive agents is also important. When this delicate balance is disrupted for any reason, mucosal injury may ensue.¹ These defensive properties appear to be mediated to a large extent by endogenous prostaglandins, nitric oxide, and trefoil proteins, and when the

synthesis of any or all are diminished, the ability of the gastroduodenal mucosa to resist injury is decreased. Thus, even normal rates of acid secretion may be sufficient to injure the mucosa and produce gastroduodenal ulcers. Nevertheless, even in DU patients who are normal secretors of acid, a reduction in the rate of acid secretion is the most efficient means of healing ulcers.¹

Although a large number of gastroduodenal ulcers are associated with *H. pylori* infection, at least 60% of individuals with complicated ulcers (e.g., hemorrhage or perforation) report the use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin.¹⁶ Mucosal injury associated with NSAID use is initiated topically by the acidic nature of NSAIDs.¹⁷ Topical mucosal injury may also occur as a result of indirect mechanisms, mediated through the biliary excretion and subsequent duodenogastric reflux of active NSAID metabolites.^{18,19} Topical injury caused by NSAIDs certainly contributes significantly to the development of gastroduodenal mucosal injury, but the systemic effects of these agents appear to play the predominant role,^{17,20,21} largely through the decreased synthesis of mucosal prostaglandins.²² Avoidance of topical mucosal injury by enteric-coated aspirin preparations²² or by the parenteral²³ or rectal²⁴ administration of NSAIDs does not prevent the development of ulcer complications. Moreover, doses of aspirin as low as 10 mg are sufficient to significantly suppress gastric mucosal prostaglandin synthesis.²⁵ A decrease in the above protective mechanisms normally stimulated by prostaglandins enables endogenous gastric acid to incite mucosal injury.

In recent years, it has become evident that the actual percentage of ulcers associated with *H. pylori* may not be 90%–95% as often reported, but may be as low as 32% in non-referral-based populations.²⁶ Furthermore, despite the inclination to ascribe the etiology of ulcers in such individuals to NSAIDs, the use of these agents clearly does not account for the balance of the cases. Finally, the vast majority of remaining individuals do not have the Zollinger–Ellison syndrome (ZES) or another unusual cause of gastroduodenal ulcer. Thus, while peptic ulceration involves the participation of several factors, as first stated by Karl Schwarz²⁷ in 1910: “*Ohne sauren Magensaft, kein peptisches Geschwür*,” i.e., “No acid, no ulcer.” The erosive properties of acid continue to play a central role in the pathogenesis of gastroduodenal mucosal ulceration, and conversely, acid suppression therapy remains the cornerstone of therapy.

GERD

Although the principal aggressive factor involved in causing heartburn and the other clinical manifestations

of GERD is the presence of acid in the esophagus, the disorder does not usually result from the hypersecretion of gastric acid.²⁸ Rather, GERD occurs as a result of several abnormalities in motor function of the lower esophagus and the lower esophageal sphincter (LES). Despite the etiologic role played by these important motor abnormalities, the severity of symptoms, most notably heartburn, and esophageal mucosal injury can be correlated with the total time that the esophageal mucosa is exposed to acid. Gastric acid thus also constitutes a critical element in the pathogenesis of GERD, and acid suppression comprises the principal mechanism for therapy. However, the optimal timing and degree of acid suppression differ significantly in GERD patients compared with the treatment of gastroduodenal ulcer (see below).

Stress-Related Erosive Syndrome

Many terms have been used to describe this entity, including stress ulcer syndrome, stress gastritis, stress-related mucosal disease, and stress-related erosive syndrome (SRES).^{29,30} The principal feature of SRES is its relationship to serious systemic disease, such as sepsis, massive burn injury, head injury associated with increased intracranial pressure, severe trauma, and multiple-system organ failure. A meta-analysis of 2252 patients by Cook et al.³¹ identified mechanical ventilation and coagulopathy as the 2 singlemost important risk factors. Although the pathophysiology is multifactorial and definitely includes a component of ischemia, which compromises gastric mucosal integrity, luminal acid plays a dominant role in producing the multiple erosive lesions characteristic of the entity. Fiddian-Green et al.³² emphasized the importance of H⁺ ion back-diffusion by demonstrating a high correlation between the degree of intramural pH and the development of SRES. Furthermore, most, but not all, methods for preventing massive hemorrhage-associated SRES include the alkalization of gastric contents.³³

Pharmacology of Parietal Cell Receptors

The parietal cell possesses a unique morphology that differs markedly between the resting and stimulated states.¹ Mitochondria occupy 34% of its cell volume, indicative of the importance of adenosine triphosphate (ATP) synthesis as an energy source required for the active transport of H⁺ ions out of the cell against a 3,000,000:1 ionic gradient. A large percentage of resting cell volume is also occupied by tubulovesicles, which are elongated tubes with smooth surface membranes, and by the

secretory canaliculus, a small invaginated area of the apical membrane. Upon stimulation, which is generally accomplished by eating a meal, the tubulovesicles decrease in number and become transformed into microvilli around the secretory canaliculus, which serves to greatly expand the surface area of the parietal cell in preparation for the secretion of large quantities of HCl. The parietal cell also possesses several different receptors for stimulatory and inhibitory ligands on its basolateral membrane (Figure 1).

Histamine H₂ Receptor and Its Antagonists

The histamine receptor belongs to a large family of G protein–linked receptors possessing 7 transmembrane domains.³⁴ Despite the recognition that histamine stimulates gastric acid secretion, it was not until 1966, when Ash and Schield³⁵ described H₁ and H₂ receptors for histamine, that the possibility of inhibiting acid secretion with histamine antagonists was proposed. In 1970, Black et al.³⁶ described selective histamine H₂-receptor inhibition and initiated the search for pharmacological agents that could effectively suppress the secretion of acid. Within 10 years of the release of cimetidine in the United States in 1977, 3 additional H₂-receptor antagonists—ranitidine, famotidine, and nizatidine—became available for use throughout the world. All 4 drugs (Figure 3) suppress basal and meal-stimulated acid secretion, albeit to a lesser degree than proton pump inhibitors (PPIs) discussed below. Despite similar therapeutic profiles, some differences do exist with regard to the agents' pharmacokinetic properties (Table 1), most of which are clinically insignificant.³⁷ The elimination of these drugs occurs by a combination of hepatic metabolism and urinary excretion, and although hepatic dysfunction does not alter their pharmacokinetic properties, dose reductions are recommended for all individuals with varying degrees of renal impairment (Table 2).³⁷ H₂-receptor antagonists as a class possess an unsurpassed

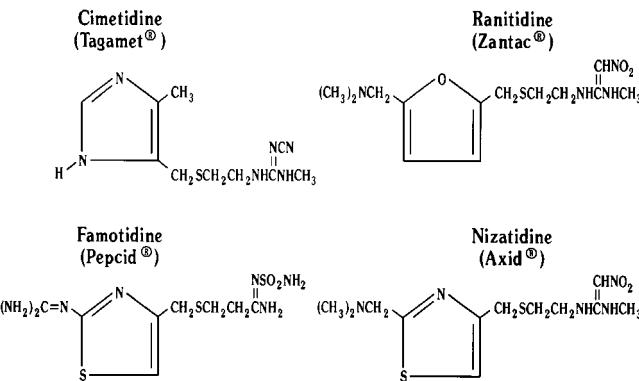


Figure 3. Structure of the 4 H₂-receptor antagonists in use in the United States.

Table 1. Comparison of the Histamine H₂-Receptor Antagonists

	Cimetidine	Ranitidine	Famotidine	Nizatidine
Bioavailability (%)	80	50	40	70
Relative potency	1	5–10	32	5–10
Circulatory t _{1/2} (h)	1.5–2.3	1.6–2.4	2.5–4	1.1–1.6
Biological t _{1/2} ^a (h)	6	8	12	8
Relative effect on cytochrome P450 metabolism	1	0.1	0	0

t_{1/2}, half-life.
^aApproximate values.
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safety record, and in 1995 became available for use in the United States without prescription.

Muscarinic Receptor and Its Antagonists

The central nervous system, particularly via the vagus nerve, plays a dominant role in regulating basal acid secretion, as well as the cephalic phase of meal-stimulated acid secretion. Extracts of belladonna were used to treat dyspepsia since the time of the Roman empire, and in the recent past, nonspecific antimuscarinic agents such as atropine and propantheline bromide were used as inhibitors of gastric acid secretion. These drugs were associated with many adverse effects, including drowsiness, dry mouth, blurry vision, and urinary retention, and as a result are rarely used today. To date, however, 5 muscarinic receptors have been subtyped and cloned, and although all are G protein coupled, they signal different intracellular pathways. In vitro characterization of gastric acid secretion has indicated that the parietal cell normally expresses the M₃ subtype.³⁸ Clinically, the M₁ antagonists, pirenzepine and telenzepine, are effective inhibitors of acid secretion and probably

Table 2. Histamine H₂-Receptor Antagonist Dosing Adjustments With Renal Insufficiency

Drug	Creatinine clearance (mL/min)	Dose (mg/day) ^a
Cimetidine	>30	800
	15–30	600
	<15	400
Ranitidine	>75	300
	30–75	225
	15–30	150
Famotidine	<15	75
	>75	40
	30–75	30
Nizatidine	15–30	20
	<15	10
	>75	300
	30–75	225
	15–30	150
	<15	75

^aDosing for gastroduodenal ulcer.
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exert their effect by interaction with a postsynaptic neuronal M_1 receptor.¹ These 2 agents are available in other countries for the treatment of duodenal ulcer, but they have not been approved for use in the United States.

Gastrin Receptor and Its Antagonists

As stated above, gastrin stimulates acid secretion via an endocrine pathway and induces H^+ ion generation both directly and indirectly. The precise location and density of the gastrin receptor have been subjects of debate and may be somewhat species dependent. Several studies in rats and other rodents have suggested that gastrin stimulates acid secretion by enhancing the release of histamine from ECL cells.^{39,40} Conversely, receptors for gastrin receptors on canine parietal cells have been demonstrated by Soll et al.⁴¹ by employing the analogue ^{125}I -[Leu¹⁵]gastrin, and by Kopin et al.,⁴² who cloned and expressed the gastrin receptor from a purified canine parietal cell complementary DNA library. Moreover, single-cell video imaging has provided direct evidence for a functional gastrin receptor on the parietal cells of rats and rabbits.⁴³

The gastrin receptor belongs to the above-mentioned family of G protein-linked receptors possessing 7 transmembrane domains.⁴² It is closely related to the receptor for cholecystokinin ("CCK-A" or "CCK-1") and is thus often referred to as the "CCK-B" or "CCK-2" receptor. Gastrin-specific receptor antagonists have been developed, which include L365,260 and YM022.⁴⁴ The former is a benzodiazepine derivative that was derived from the fungus *Aspergillus alliaceus* and has been demonstrated to effectively antagonize gastrin-stimulated gastric acid secretion.⁴⁴ Despite this effect, these antagonists have not been used clinically as inhibitors of acid secretion. However, they may ultimately prove useful in the treatment of panic and anxiety disorders by virtue of binding to gastrin receptors in the brain.⁴⁵

Miscellaneous Receptors on the Parietal Cell

Other receptors on the parietal cell basolateral membrane have been suggested by the ability of various agents to inhibit gastric acid secretion. For example, prostaglandins inhibit H^+ ion generation by binding to their EP3 G protein-linked receptor on the parietal cell, which appears to inhibit adenylate cyclase, and thereby decrease intracellular cAMP generation when activated.⁴⁶ As discussed below, the acid-inhibitory properties of prostaglandin analogues such as misoprostol, while not potent, are nevertheless critical for exerting any beneficial clinical effects.¹⁶

Parietal Cell H^+,K^+ -Adenosine Triphosphatase

The gastric enzyme H^+,K^+ -adenosine triphosphatase (ATPase) is a member of the family of ion-motive ATPases that includes F_1 , V, and P ATPases. The latter is divided conveniently into P_1 or P_2 types in 1 of 2 ways, either based on the number of transmembrane segments (8 in the case of the P_1 and 10 in the case of the P_2 catalytic subunits) or based on transport of transition metals (P_1) or small cations (P_2).⁴⁷ Within the P_2 family, the gastric H^+,K^+ - and Na^+,K^+ -ATPase isoforms are coexpressed tightly bound to a β -subunit that is smaller than the catalytic or α -subunit, has most of its sequence presented outside, and is glycosylated to different extents depending on the isoform.^{48,49} These latter 2 enzymes are also unique in that they both serve as drug targets, digoxin for congestive heart failure in the case of the Na^+,K^+ -ATPase and substituted pyridyl methylsulfinyl benzimidazoles for acid-related disorders in the case of the H^+,K^+ -ATPase.⁵⁰ H^+,K^+ -ATPase consists of 8 transmembrane segments for the catalytic α -subunit and 1 transmembrane segment for the β -subunit (Figure 4).^{51,52}

Inhibition of Acid Secretion

The recognition that the ATPase was the final step of acid secretion has resulted in the development of a class of drugs, the PPIs, that are targeted toward this enzyme. They all share a common structural motif (Figure 5), a substituted pyridylmethylsulfinyl benzimidazole, but vary in terms of their substitutions. They also share common inhibitory mechanisms and are all weak protonatable pyridines, with a pK_a of ~ 4.0 for omeprazole, lansoprazole, and pantoprazole, and ~ 5.0 for rabeprazole. They thus accumulate selectively in the acid space of the secreting parietal cell. Within that space or on the surface

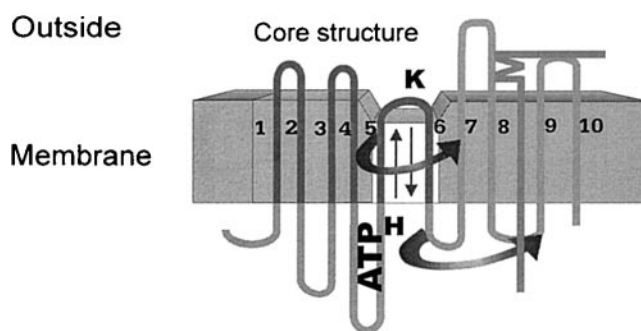


Figure 4. A model of the 2-dimensional arrangement of the gastric H^+,K^+ -ATPase subunits. The core structure of this P_2 -type ATPase consists of the first 6 membrane segments, arranged as helices with the possible exception of the cytoplasmic end of M6. Cross-linking and column chromatography of tryptic fragments has shown an association between M5 and M7, and M6 and M9 (curved arrows). The major high-affinity interaction with the β -subunit is with the beginning of M8.

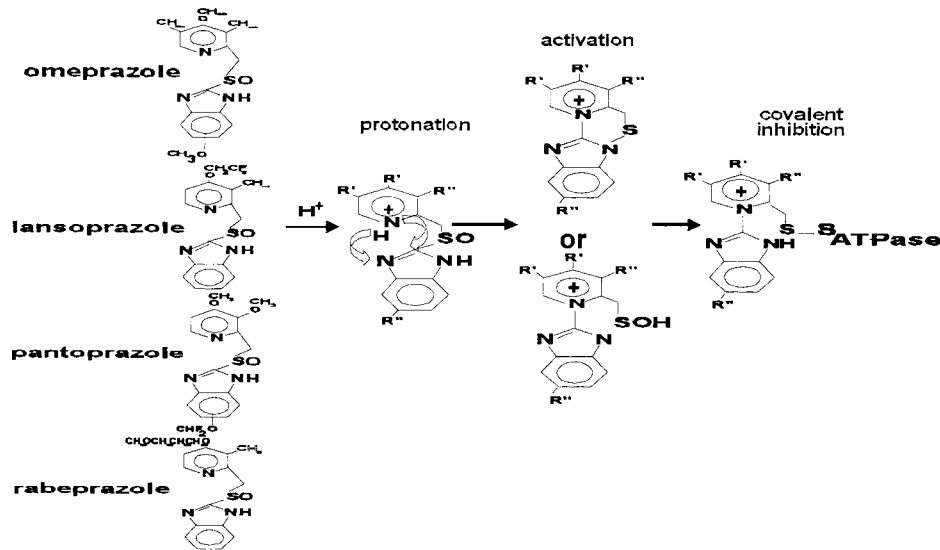


Figure 5. Structure and reaction pathways of the 4 PPIs in use in the United States. All are ampholytic weak bases and accumulate as prodrugs in the secretory canaliculus of the actively secreting parietal cell. They are all acid-catalyzed to a reactive thiophilic species whereby the pyridine N reacts with the 2C of the benzimidazole to form a sulfenic acid (below), which, while in solution, reacts further to form a sulfenamide (above). The respective sulfenamides then react with available cysteines on the luminal surface of the enzyme; cys 813 is common to all the PPIs and crucial for enzyme inhibition. Cys 892 reacts with omeprazole, lansoprazole, and rabeprazole; cys 321 with lansoprazole; and cys 822 with pantoprazole.⁵⁴

of the enzyme, they undergo an acid-catalyzed conversion to a reactive species, the thiophilic sulfenamide or sulfenic acid, which are permanent cations. The rate of conversion varies among the compounds and is a function of their pK_a and other structural features: rabeprazole > omeprazole = lansoprazole > pantoprazole.^{53,54} The reactive species reacts with cysteine residues available from the external surface of the enzyme that faces the lumen of the secretory space of the parietal cell, resulting in covalent inhibition of the enzyme by disulfide bond formation. The cysteine residue that is critical for inhibition is cys 813 in the catalytic subunit of the $H^+,K^+-ATPase$, strategically located in the M5/M6 sector of the enzyme, which is intimately involved in the transport process.

Because all the PPIs require accumulation and acid activation, their onset of inhibition is delayed, and because they also form a covalent derivative, the restoration of acid secretion is likewise delayed, depending on the turnover of the pump protein and the biological reversibility of the disulfide bond. Therefore, 24–48 hours are necessary for maximal acid secretory capacity to be restored. Different doses of these drugs are recommended, but at equivalent doses, these agents are remarkably similar when used in the treatment of acid-related disorders (Table 3).⁵⁵

The PPIs are without question the most potent inhibitors of gastric acid secretion available. However, because they are most effective when the parietal cell is stimulated to secrete acid in response to a meal, these

drugs should *only* be taken before or with a meal and should *not* be used in conjunction with H_2 -receptor antagonists, prostaglandins, or other antisecretory agents (Table 3). Animal studies have demonstrated that the concomitant administration of PPIs and other antisecretory agents will markedly reduce the acid-inhibitory effects of the PPI.⁵⁶ Because acid secretion must be stimulated for maximum efficacy, PPIs are administered before the first meal of the day (Table 3). Moreover, in

Table 3. Helpful Facts on the Use of PPIs

PPIs are prodrugs that require activation to their active moiety (thiophilic sulfenamide)
pK_a of PPIs: ~4 for omeprazole, lansoprazole, and pantoprazole; ~5 for rabeprazole
All PPIs are activated when regional pH decreases below their respective pK_a
Achieved almost exclusively in parietal cell secretory canaliculus
Achieved optimally when parietal cell is activated, i.e., after meals
Most effective after a prolonged fast, when a large amount of inactive $H^+,K^+-ATPase$ present is in secretory canaliculus, i.e., after breakfast
Clinical use
Steady state not achieved for several days
Thus often helpful to administer twice daily for the first 2–3 days of therapy
Also likely not to be consistently clinically effective when taken sporadically
First dose should be taken before breakfast
Second dose, if used, should be taken before evening meal
Do not administer concomitantly with H_2 -receptor antagonists or prostaglandins
Safety: toxicity seems to be gastrin-related and is probably species specific

most individuals, once-daily dosing is sufficient to produce the desired level of acid inhibition. A second dose, if required, should be administered before the evening meal.

During meals, however, neither all parietal cells nor all proton pumps are active. The initial dose of the PPI will thus inhibit only activated H^+, K^+ -ATPase present in the canalicular membrane.⁵⁶ As inactive enzyme is recruited into the secretory canaliculus, acid secretion will resume, albeit at a reduced level. After a second dose, more enzyme will have been recruited and subsequently inhibited, and after a third dose, additional recruitment and further acid inhibition may be expected. Once-daily PPI dosing results in 66% steady-state inhibition of maximal acid output after 5 days, and the initial use of twice-daily dosing (for the first 2–3 days) may thus be helpful in achieving more rapid inhibition of gastric acid secretion.⁵⁵ Based on these pharmacokinetic properties, the occasional use of a PPI taken on an “as-needed” basis would not be expected to provide adequate acid inhibition and would be unlikely to produce a consistent or satisfactory clinical response.

Safety Issues

The safety profile of the PPIs is similar to that of H_2 -receptor antagonists. Although headache and diarrhea are occasionally reported, serious adverse reactions to these agents are rare and generally not well documented. Initial concern was expressed when PPIs were introduced as a result of their ability to precipitate ECL cell hyperplasia and subsequent gastric carcinoid tumors in rats when given at high doses. This trophic effect occurs as a result of interruption of the negative feedback mechanism for acid secretion, which induces an increase in antral gastrin gene expression.^{1,4–6} However, these drugs have been used for nearly 15 years in Europe and for 10 years in the United States with no discernible increase in the incidence of carcinoid tumors. The reasons for such interspecies differences are not entirely evident, but are probably related in part to a lower mucosal ECL cell density and a considerably less pronounced increase in circulating gastrin in humans compared with rodents in response to antisecretory medications. One area of theoretical concern that has not been completely resolved is the possible effect of gastrin and its precursor proghormone on promoting the growth of colonic neoplasms.

An area of controversy has been the need to monitor serum gastrin concentrations in persons on long-term PPI therapy. In general, laboratory and other testing should be performed only if the treatment plan will be dependent on their results. Long-term PPI treatment is used most commonly in patients with GERD, many of

whom have significant symptoms and mucosal injury. The sequelae of GERD are serious and real, whereas the effects of hypergastrinemia, which occurs in only ~5% of individuals receiving long-term PPI therapy, are theoretical. Therefore, in situations in which the hypothetical risk of the PPI is clearly outweighed by the benefits offered by potent acid suppression, serum gastrin measurements should not be performed.⁵⁷

Treatment of Acid-Related Disorders

Acute Gastroduodenal Ulcer

The treatment of ulcer disease has changed dramatically since the discovery that the probability of ulcer recurrence decreases significantly after successful eradication of *H. pylori* infection, compared with annual recurrence rates of 50%–80% when antisecretory therapy alone is used.^{58,59} Thus, a determination of *H. pylori* infection in a patient with gastroduodenal ulcer is critical for the appropriate management of this disease. If a patient is not infected with *H. pylori*, an alternative etiology must be sought, such as NSAID use, hypersecretory states, or one of the other less common causes of ulcer disease, such as Crohn's disease, vascular insufficiency, viral infection, radiation therapy, and cancer chemotherapy. Regardless of the etiology, however, the inhibition of gastric acid secretion continues to play a prominent role in the management of acute gastroduodenal ulcer.

Some differences do exist between DUs and GUs proximal to the prepyloric region of the stomach. Most previous studies have assessed the effects of acid suppression on duodenal and pyloric channel ulcers and antral ulcers within 2–3 cm of the pylorus, but few have actually evaluated the healing of more proximal GUs. Although gastric acid secretion is generally lower than normal in patients with more proximal disease,¹ these latter ulcers usually do heal in response to acid suppression, although the total duration of therapy is often prolonged.

In general, a dynamic relationship exists between the healing of DU and the inhibition of intragastric acidity. Important parameters that determine the effect of antisecretory therapy include the degree of suppression of intragastric acidity, the length of acid inhibition over a 24-hour period, and the duration of antisecretory treatment. For example, Burget et al.⁶⁰ showed that if intragastric pH is maintained above 3.0 for a period of 18–20 hours per day, DU healing approximates 100% at 4 weeks. As discussed below, the DU healing rate at 4 weeks is also directly proportional to the degree of the reduction of nocturnal acidity.⁶¹

Table 4. Current Recommendations for Treatment of Gastroduodenal Ulcers

Active ulcer	
H ₂ -receptor antagonists	
Cimetidine 800 mg	
Ranitidine/nizatidine 300 mg	
Famotidine 40 mg	
All administered between the evening meal and bedtime	
PPIs	
Omeprazole 20 mg	
Lansoprazole 30 mg	
Rabeprazole 20 mg	
Pantoprazole 40 mg	
All administered daily before breakfast	
Maintenance therapy	
H ₂ -receptor antagonists	
Cimetidine 400 mg	
Ranitidine/nizatidine 150 mg	
Famotidine 20 mg	
All administered between the evening meal and bedtime	
PPIs	
As above	
Prevention of NSAID-induced ulcers	
Misoprostol	
At least 200 µg 3 times/day	
PPIs	
As above	

NOTE. In general, duodenal ulcers should be treated for 4 weeks and gastric ulcers for 8 weeks.

Antacids. In a landmark controlled, double-blind study in 1977, Peterson et al.⁶² showed that antacids were superior to placebo in healing DU, although (contrary to prevailing opinions) no difference in symptom relief was detected. However, because of the need to take these drugs at least 4, and up to 7, times every day, antacids are rarely used presently in the healing of gastroduodenal ulcers.

H₂-receptor antagonists. These agents (Figure 3) are specific antagonists that inhibit gastric acid secretion competitively and reversibly by blocking the histamine receptor on the parietal cell basolateral membrane. They only partially inhibit acid secretion stimulated by gastrin and are more effective in suppressing intragastric acidity during periods of basal acid secretion. However, DU healing is directly proportional to the degree of the reduction of nocturnal acidity, and because the longest period of basal acid secretion occurs during the night,⁶¹ the optimal time for dosing H₂-antagonists in the treatment of DU is between the evening meal and bedtime (Table 4). These drugs promote healing in ~70%–80% of patients after 4–6 weeks compared with placebo healing rates of 20%–45%.

Reports in the literature are conflicting regarding the superiority of one H₂-antagonist over another in healing DUs. McIsaac et al.⁶³ performed a meta-analysis of 44 clinical trials involving more than 4300 patients to compare DU healing with 4 weeks of ranitidine, 150 mg

twice daily, and cimetidine, 400 mg twice daily or 1 g/day. They found a significant difference between the 2 agents, with overall healing 7% greater in the ranitidine group. However, multidose regimens have been largely replaced by a single evening-dose regime (with an equivalent total daily dose), which takes advantage of the observation that ulcer healing is proportional to the effectiveness of nocturnal acid secretion. In a large American multicenter trial, Gitlin et al.⁶⁴ found that 40 mg famotidine twice daily was equivalent to 40 mg of the drug given only once at bedtime in promoting DU healing. In several subsequent comparative trials, 40 mg famotidine and 300 mg nizatidine at bedtime have been found to have an effect similar to ranitidine in healing both DU and GU, with healing of 55%–65% of GU and 73%–75% of DU at 4 weeks.^{65,66} Thus, as stated above, it is now recommended that all H₂-receptor antagonists be administered between the evening meal and bedtime (Table 4) in the treatment of gastroduodenal ulcer. It also appears reasonable to recommend 4 and 8 weeks of therapy for acute DU and GU, respectively.

PPIs. As discussed below, in addition to their use in the treatment of gastroduodenal ulcers caused by *H. pylori*, PPIs are the agent of choice for the treatment of ZES and for healing ulcers associated with the use of NSAIDs. PPIs appear to heal gastroduodenal ulcers more rapidly than H₂-receptor antagonists. In a meta-analysis comparing the healing of DU, Holt and Cowden⁶⁷ reported that omeprazole, 20 mg every morning for 4 weeks, was superior to both 300 mg ranitidine and 800 mg cimetidine, both administered at bedtime (Figure 6). Similarly, in another meta-analysis, Poynard et al.⁶⁸ found that lansoprazole, 30 mg every morning, healed significantly more ulcers than 300 mg ranitidine and 40 mg famotidine, both administered at bedtime. The

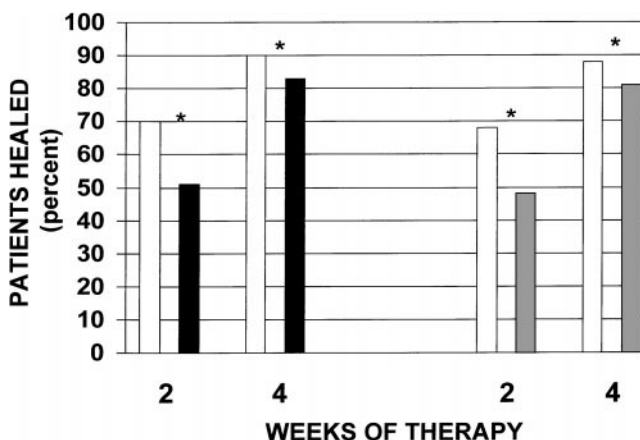


Figure 6. Meta-analysis comparing duodenal ulcer healing at 2 and 4 weeks with 800 mg cimetidine (□) or 300 mg ranitidine (■), both administered at bedtime, with 20 mg omeprazole daily (□). **P* < 0.001. Data from Holt and Howden.⁶⁷

pooled healing rates were 60% and 85% for lansoprazole at 2 and 4 weeks, respectively; the corresponding figures for the H₂-antagonists were 40% and 75%.⁶⁸ Rabeprazole⁶⁹ and pantoprazole⁷⁰ have also demonstrated superior and accelerated DU healing compared with H₂-receptor antagonists. PPIs also appear to heal GUs more rapidly and at a greater rate than H₂-blockers. For example, Bader and Delchier⁷⁰ reported that pantoprazole healed 32% and 15% more GUs at 4 and 8 weeks, respectively, than ranitidine. While clearly more effective, as will be discussed below, the margin of benefit conferred by PPIs over H₂-antagonists in the healing of ulcers is far smaller than the advantage offered by these agents in the treatment of GERD. Moreover, like the H₂-blockers, the optimal duration of therapy with PPIs should be 4 and 8 weeks of therapy for acute DU and GU, respectively. The dosing of PPIs in the treatment of gastroduodenal ulcer is summarized in Table 4.

In summary, nearly all peptic ulcers will eventually heal, as evident by the placebo responses in the above-mentioned studies. Antisecretory therapy accelerates the healing process and allows for more rapid relief of symptoms. Antacids, H₂-receptor antagonists, and PPIs have similar healing rates when given for at least 4 weeks, although the latter agents appear to heal ulcers more rapidly and to a greater extent than the others. Moreover, because PPIs are commonly used in *H. pylori* eradication regimens and because they heal gastroduodenal ulcers in patients continuing NSAID use, they have become, and will likely remain, the mainstay of therapy for healing gastroduodenal ulcers.

The Role of Maintenance Therapy in Gastroduodenal Ulcer

The natural history of PUD has changed significantly with the recognition that eradication of *H. pylori* infection in DU patients greatly diminishes the relapse rate. Graham et al.⁷¹ showed that after a median follow-up of 38 weeks, only 12% of patients who underwent *H. pylori* eradication relapsed, compared with 95% of patients who received H₂-receptor antagonists alone. Other studies report similar relapse rates after *H. pylori* therapy, so that the maxim "once an ulcer, always an ulcer" no longer holds true.

Accordingly, the role of maintenance antisecretory therapy has changed in recent years. Before embarking on long-term therapy, careful attention must be paid to the elimination of the most important risk factors for ulcer recurrence: *H. pylori* infection and NSAID use. Several studies have demonstrated the cost-effectiveness of *H. pylori* eradication compared with maintenance antisecretory therapy, which may cost up to \$1200 per year.⁷² In

general, only high-risk ulcer patients should be considered as candidates for maintenance antisecretory therapy. This group includes patients with a history of ulcer complications, those who have frequent recurrences, those who are *H. pylori* negative, and those who fail to clear *H. pylori* infection despite appropriate therapy. However, even patients who have had a complicated ulcer may not require maintenance therapy, provided *H. pylori* infection is cured.^{73,74} Maintenance therapy regimens include an H₂-receptor antagonist administered at bedtime at one half the dose required for initial healing or a PPI taken before breakfast (Table 4).

Role of Acid Inhibition in Healing NSAID-Induced Gastroduodenal Ulcers

The optimal treatment for patients with NSAID-induced gastroduodenal ulcers is the discontinuation of any potentially aggravating factors. If NSAID use must be continued, however, the capacity to heal ulcers varies among the various antisecretory agents.

H₂-receptor antagonists. Several open, uncontrolled, nonrandomized studies⁷⁵ and prospective, randomized studies⁷⁶ have suggested that treatment with conventional doses of H₂-receptor antagonists for 6–12 weeks results in healing of ~75% of GUs and 85% of DUs despite the continued use of NSAIDs. When NSAID use is continued, healing appears to be delayed and is largely dependent on the initial ulcer size. O'Laughlin et al.⁷⁷ reported a 90% healing rate of small GUs (<5 mm in diameter) after an 8-week course of cimetidine treatment, while only 25% of ulcers >5 mm in diameter healed.

PPIs. Recently, Hawkey et al.⁷⁸ compared the capacity of misoprostol (200 µm 4 times daily) and omeprazole (20 mg or 40 mg daily) to heal gastroduodenal ulcers in patients continuing NSAID therapy (OMNIUM Study). After 8 weeks of therapy, omeprazole at both doses healed 89% of the DUs, whereas only 77% of DUs in those receiving misoprostol were healed. GU healing was detected in 80%, 87%, and 73% of those receiving 40 mg omeprazole, 20 mg omeprazole, and misoprostol, respectively.⁷⁸

In a recent multicenter trial by Yeomans et al. (ASTRONAUT Study)⁷⁹ in a group of 541 patients, the superiority of omeprazole over ranitidine in treatment of NSAID-related gastroduodenal ulcers was demonstrated. Ulcer healing rates at 8 weeks were 79%, 80%, and 63% in those receiving 40 mg omeprazole, 20 mg omeprazole, and 150 mg ranitidine twice daily, respectively. Another study by Agrawal et al.⁸⁰ compared the efficacy of lansoprazole and ranitidine in healing of GUs in patients continuing NSAID therapy. After 8 weeks, ulcers were healed in 57% of individuals receiving 150 mg ranitidine

twice daily, while healing rates were 73% and 75% in those treated with 15 and 30 mg lansoprazole (each once daily), respectively. These observations indicate that PPIs have the capacity to heal gastroduodenal ulcers at an accelerated rate whether or not NSAID use is continued. Although ulcer healing is possible with H₂-receptor antagonists and antisecretory doses of misoprostol, the above studies indicate that the more potent inhibition of gastric acid secretion provided by PPIs enhances their healing properties (Table 4).

Prophylaxis of NSAID-Associated Gastroduodenal Ulcers

Because of the number and serious nature of NSAID-related GI complications, recent efforts have been directed at the prevention of mucosal injury induced by NSAIDs. Although the optimal means of minimizing this risk is to avoid NSAIDs and substitute with a less toxic agent, NSAID use is commonly preferred. Two strategies have thus been used to prevent ulcers: the use of concomitant medication and the development of safer anti-inflammatory agents, such as the cyclooxygenase 2-specific inhibitors and nitric oxide-releasing NSAIDs. The use of these latter agents has been reviewed recently^{16,81} and will not be discussed below. Because dyspeptic symptoms are not a reliable warning sign for the development of serious NSAID-related mucosal injury,¹⁶ it is important to identify patients who are more likely to suffer adverse consequences with NSAID therapy. Advanced age has been consistently found to constitute one of the primary risk factors for adverse GI events and appears to increase in a linear fashion.¹⁶ Contrary to previous reports suggesting adaptation with time, recent studies indicate that the risk of NSAID-associated GI hemorrhage remains constant over an extended period of observation.⁸² Other risk factors include high NSAID doses, prior history of gastroduodenal ulcer and gastrointestinal bleeding, use of concomitant corticosteroids, significant comorbid conditions, and coadministration of anticoagulants.¹⁶ However, many of these studies are based on univariate analysis and do not consider the interactions among multiple factors and comorbidities.

The identification of *H. pylori* as an etiologic factor in the development of peptic ulcer has raised the question of a possible synergistic relationship between the presence of this organism and NSAID use in the development of gastroduodenal mucosal injury. Most,^{83–86} but not all,^{87,88} studies have found these 2 risk factors to be independent. For example, Chan et al.⁸⁸ found that eradication of *H. pylori* using a regimen that included bismuth subcitrate significantly decreased the occurrence of ulcers associated with the use of naproxen. In this study, ulcers developed

in 26% of *H. pylori*-infected individuals but in only 7% of persons successfully treated with antimicrobial therapy. While provocative, the inclusion of bismuth in the drug regimen conferred a level of ambiguity to this study because of the ability of bismuth to accumulate in the gastric mucosa and stimulate prostaglandin synthesis.⁸⁹ Most recently, Hawkey et al.⁹⁰ randomized 285 patients with current or previous ulcers receiving NSAIDs to therapy with omeprazole, clarithromycin, and amoxicillin or omeprazole alone and found that although *H. pylori* eradication did not affect the rate of ulcer recurrence, gastric ulcer healing was *impaired* in those individuals successfully treated. It thus appears that *H. pylori* infection increases the risk of gastroduodenal injury associated with NSAID use only minimally, if at all.¹⁶

H₂-receptor antagonists. Two large placebo-controlled, prospective trials investigated the protective effect of ranitidine in arthritis patients receiving concomitant NSAID therapy.^{91,92} Ranitidine, 150 mg twice per day, proved to be effective in preventing DUs, with rates of 0% and 1.5% in the 2 studies, compared with 8% in placebo-treated patients. In contrast, ranitidine at this dose was ineffective in preventing GUs in both studies. Taha et al.⁹³ recently reported a beneficial effect of high-dose famotidine (40 mg twice per day) in preventing both gastric and DUs in arthritis patients receiving NSAIDs for 24 weeks. Although symptomatic relief was also observed in the group randomized to famotidine, the beneficial effect, although statistically significant, was modest, and the cost associated with such doses of H₂-receptor antagonists is considerable. Thus, the use of H₂-receptor antagonists in the prevention of NSAID-associated ulcers cannot be recommended.

PPIs. In addition to examining ulcer healing, the recent ASTRONAUT study also compared omeprazole and ranitidine in the prevention of recurrent gastroduodenal ulcer in a large number of arthritic individuals in whom ulcers had healed and NSAID therapy was continued. A group of 432 patients was randomly assigned to treatment with either 20 mg omeprazole once daily or 150 mg ranitidine twice daily.⁷⁹ At the end of 6 months, 16.3% and 4.2% of those given ranitidine developed gastric and DUs, respectively, while only 5.2% developed a GU and 0.5% a DU in the omeprazole group.⁷⁹

In the recent OMNIUM study, the capacity of omeprazole and misoprostol in preventing ulcer recurrence was compared in arthritic individuals continuing NSAID therapy.⁷⁸ In this double-blind, placebo-controlled trial, 732 patients in whom ulcers had healed were randomized to receive either placebo, 20 mg of omeprazole once daily, or 200 µm of misoprostol twice per day as maintenance therapy. After 6 months, DUs were detected in 12% and

10% of those treated with placebo and misoprostol, respectively, while only 3% of those treated with omeprazole developed a DU. Gastric ulcer relapse occurred in 32%, 10%, and 13% of the individuals receiving placebo, misoprostol, and omeprazole, respectively.⁷⁸ These studies suggest that PPIs are superior to H₂-receptor antagonists in maintaining patients in remission during continued NSAID use,^{16,94} as well as in improving dyspeptic symptoms associated with the use of NSAIDs.

Prostaglandins. As discussed above, although not potent antisecretory agents, the acid-inhibitory properties of misoprostol appear to be critical for exerting its beneficial clinical effects. In their initial study, Graham et al.⁹⁵ reported that the prevalence of GUs in osteoarthritis patients who were receiving NSAIDs was 1.4% in those concomitantly taking 200 µm misoprostol 4 times daily, 5.6% receiving 100 µm misoprostol 4 times daily, and 21.7% receiving placebo. The efficacy of misoprostol in DU prophylaxis was confirmed in another study by Graham et al.⁹⁶ In this group of 638 patients, misoprostol significantly reduced the incidence of DUs from 4.6% in those taking placebo to 0.6% in those receiving 200 µm misoprostol 4 times daily. Because of the dose-dependent adverse effects of this agent, Raskin et al.⁹⁷ conducted a study to evaluate 3 different regimens (200 µm twice, 3 times, and 4 times daily). Their study indicated that, although lower doses of misoprostol are better tolerated, the drug must be taken at least 3 times a day to provide significant prophylaxis for NSAID-induced GUs. Finally, Silverstein et al.⁹⁸ conducted the Misoprostol Ulcer Complication Outcomes Safety Assessment (MUCOSA) trial and observed a 40% reduction in overall complications from NSAID-associated ulcers in individuals taking 200 µm misoprostol 4 times per day.⁹⁸

Despite being a highly effective form of therapy for preventing NSAID-induced ulcers and the only drug approved by the Food and Drug Administration (FDA) for prophylaxis against NSAID-related gastroduodenal ulcers, misoprostol is associated with a significant number of adverse effects, including dose-related diarrhea and spontaneous abortion. Presently, it thus appears that after an NSAID-related gastroduodenal ulcer is healed and it is determined that NSAID use must be continued, recurrent ulceration may be prevented either by the use of a cyclooxygenase 2-specific inhibitor, such as celecoxib or rofecoxib, or concomitant administration of misoprostol (at least 200 µm 3 times daily) or a PPI (Table 4).^{16,81} However, it must be stressed that, despite the marked efficacy of PPIs in improving dyspeptic symptoms and preventing endoscopic ulcers caused by NSAID use,^{16,81,94} prospective clinical outcome analyses have not yet been performed to assess the ability of PPIs to prevent

NSAID-related ulcer complications. Likewise, studies aimed at determining the most cost-effective means of approaching the significant issue of NSAID-related GI toxicity have not yet been performed.

ZES

Although concern for patients with ZES initially revolved around massive hyperchlorhydria and virulent peptic ulceration, the availability of potent inhibitors of acid secretion refocused attention on the malignant potential of the gastrinoma.^{99,100} The goal of therapy in patients with ZES is surgical extirpation of all tumor, which is possible in ~50% of individuals with sporadic gastrinoma. A recent study by Norton et al.⁹⁹ confirmed the inability to successfully maintain individuals with familial forms (multiple endocrine neoplasia type I) in a disease-free state for prolonged periods. These patients require potent acid suppression for an indefinite period. Moreover, all patients with ZES, whether sporadic or familial, require antisecretory therapy after the diagnosis is established and during initial evaluation as attempts are made to localize the gastrinoma.

Patients with ZES should be treated initially with a PPI, using twice the dose normally employed to treat gastroduodenal ulcers associated with *H. pylori* infection or NSAID use (e.g., 40 mg omeprazole or 40 mg rabeprazole, 60 mg lansoprazole, or 80 mg pantoprazole, all administered before breakfast).¹⁰⁰ The relief of epigastric pain does not reliably predict the absence of mucosal injury,¹⁰¹ although the relief of all symptoms associated with ZES, including heartburn and diarrhea, is desirable. The only parameter to reliably predict gastroduodenal mucosal injury is the level of acid inhibition. After a steady state has been achieved, basal acid output should be measured 1 hour before the next dose of the PPI is to be administered. The goal of therapy is not achlorhydria, but rather a basal acid output of 1–10 mmol/h.¹⁰¹ If complete inhibition of acid secretion is evident, the PPI dose should be decreased by 50% and the patient reassessed. If the basal acid output is >10 mmol/h, the dose should be increased incrementally, and for doses >60 mg of omeprazole (or an equivalent dose for the other PPIs), the PPI should be divided and one half given before breakfast and one half before dinner. Patients should be evaluated periodically (every 6–12 months) and dose adjustments made accordingly. In contrast to the H₂-receptor antagonists, which are now rarely used for the treatment of the ZES because of tachyphylaxis associated with their prolonged use, the need to increase the PPI dose is necessary in only ~10% of ZES patients.¹⁰¹

GERD

Therapy for GERD can be approached in 2 different fashions. The correction of the mechanisms involved in the pathogenesis of GERD includes a decrease in the frequency of transient LES relaxations and an improvement of esophageal clearance to minimize the exposure of the esophagus to acidic gastric contents. The more commonly used approach, however, employs the neutralization or suppression of intragastric acidity, whereby, despite the continued reflux of gastric contents into the esophagus, the refluxate is rendered nonirritating to the esophageal mucosa (Table 5). This approach not only provides symptomatic relief, but also treats and prevents mucosal injury.

Antacids. Antacids have been used since the time of the ancient Greeks, who used coral powder (containing calcium carbonate) to treat various digestive maladies. Before the introduction of cimetidine in the mid-1970s, they comprised the mainstay of therapy for GERD. Although a few old studies compared antacids with cimetidine in the treatment of esophagitis,^{102,103} these drugs are now used exclusively to treat mild episodic heartburn and are rarely prescribed. When used by individuals for the treatment of heartburn, they offer the advantage of prompt, although often unsustained, relief.

Histamine H₂-receptor antagonists. The H₂-receptor antagonists are used extensively for GERD, both in over-the-counter and prescription formulations. Early studies of the efficacy of these drugs were disappointing, largely because they were performed using doses commonly employed to treat PUD. It is now recognized that GERD requires higher doses of H₂-antagonists to effectively treat this disorder. A randomized, controlled trial of cimetidine, 800 mg twice daily for 12 weeks, showed

symptom relief and mucosal healing in 67% of patients, compared with 36% in the placebo arm.¹⁰⁴ Similar studies of famotidine showed 12-week healing rates of 75% for dosing 20 mg twice daily and 66% for dosing 40 mg at bedtime.¹⁰⁵ Other studies show comparable results, with 50%–75% rates of symptom relief and healing. The rates of healing are clearly related to the initial severity of esophagitis, with rates for grade I–II esophagitis approaching 80%, and rates of only 30%–50% with grade III–IV disease.¹⁰⁶ The timing of drug administration is also important. In patients with erosive GERD, most reflux episodes occur between the evening meal and midnight, and in mild GERD, nocturnal acid suppression may be as effective as multiple daily doses. Studies comparing nocturnal with twice-daily dosing show 80%–90% healing rates for grade I disease, 60%–70% for grade II, and 40%–50% for grade III.^{105,107,108} Thus, patients with grade I esophagitis may benefit from once-daily dosing after dinner or bedtime, but patients with higher grades of disease will generally require multiple doses per day. In all cases, however, individualization of therapy must be considered.

PPIs. Numerous studies have documented the efficacy of PPIs in controlling GERD symptoms and healing esophagitis. Pooled data from 3 studies including 653 patients treated with lansoprazole, 30 mg daily, in patients with grade II or worse esophagitis showed 80%–90% healing at 4 weeks and 92% healing at 8 weeks.^{109–111} Comparative trials of PPIs and H₂-antagonists show a clear advantage with the former agents. One trial comparing lansoprazole, 30 mg daily, and ranitidine, 300 mg twice daily, in patients with moderate-to-severe erosive GERD showed 91% healing in 8 weeks with lansoprazole compared with 66% healing for ranitidine.¹¹² PPIs are also effective in patients with GERD unresponsive to high-dose H₂-blocker therapy. In patients refractory to cimetidine, 800 mg 4 times daily, or ranitidine, 300 mg 3 times daily, therapy with 40 mg omeprazole in the morning healed esophagitis in 91% of patients studied.¹¹³

In general, standard doses of PPIs (20 mg omeprazole, 30 mg lansoprazole, 20 mg rabeprazole, or 40 mg pantoprazole, all administered before breakfast) will relieve symptoms and heal esophagitis in approximately 85%–90% of cases (Table 5). In a large meta-analysis, Chiba et al.¹¹⁴ clearly demonstrated the superiority of PPIs over H₂-receptor antagonists in both relieving symptoms and in healing esophagitis. In nonresponders, a careful history regarding the timing of PPI administration should be obtained. As stated above, the optimal time is immediately before breakfast. Once the correct timing is established, a second dose of the PPI (before the

Table 5. Antisecretory Drug Regimens for Treatment of GERD

H₂-receptor antagonists

Nonerosive GERD

- Cimetidine 400 mg twice/day
- Ranitidine/nizatidine 150 mg twice/day
- Famotidine 20 mg twice/day
- Therapy should be individualized to fit patient requirements; often effective when administered between breakfast and lunch, and between the evening meal and bedtime

Erosive GERD

- Cimetidine 400 mg every 6 h
- Ranitidine/nizatidine 150 mg every 6 h
- Famotidine 40 mg every 12 h

PPIs

Nonerosive or erosive GERD

- Omeprazole 20 mg daily or 20 mg twice/day
- Lansoprazole 30 mg daily or 30 mg twice/day
- Rabeprazole 20 mg daily or 20 mg twice/day
- Pantoprazole 40 mg daily or 40 mg twice/day
- All administered daily before breakfast; second dose, if necessary, should be given before evening meal

evening meal) should be attempted initially before substituting with another PPI. If symptoms persist, patients should undergo an endoscopic evaluation, and pH monitoring while on medication should be considered to confirm the presence of acid reflux and to assess the ability of the medications in effectively suppressing acid secretion. Peghini et al.¹¹⁵ have advocated the use of H₂-receptor antagonists at bedtime in such patients. This practice may be useful in some individuals, but caution must be exercised because of the undesirable effects of H₂-antagonists on PPI activation discussed above. If the use of H₂-blockers is being contemplated under such circumstances, it is preferable to use a short-acting agent to avoid any such interference. Truly refractory patients should be referred for consideration for antireflux surgery or experimental endoscopic forms of therapy.

Because GERD is a chronic disorder, maintenance therapy has also emerged as an important issue in the management of patients with the disease. Most patients with GERD, especially those with grade III and IV esophagitis, will relapse once therapy is discontinued.¹¹⁶ In addition, maintenance of remission usually requires the same type and dose of medication that healed the initial esophagitis. A landmark study by Vigneri et al.¹¹⁷ of maintenance therapy compared 5 regimens: ranitidine, cisapride, ranitidine plus cisapride, omeprazole, and omeprazole plus cisapride (Figure 7). All patients (n = 175) had esophagitis on initial endoscopy and were treated with 40 mg omeprazole daily for 8 weeks before starting one of the maintenance regimens (n = 35 for each group). After 12 months of treatment, remission was maintained in 80% of the omeprazole group vs. 54% in the cisapride and 49% in the ranitidine groups. Ranitidine plus cisapride was significantly better than ranitidine alone (66% remission), and the combination of

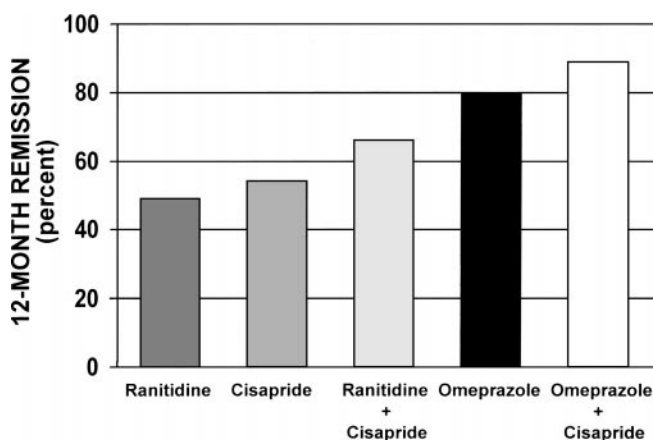


Figure 7. Comparison of 5 regimens used as maintenance therapy in patients with erosive GERD. Data represent the mean percentage of patients in remission after 12 months of therapy. Data from Vigneri et al.¹¹⁷

omeprazole plus cisapride was best of all, with an 89% remission rate; however, the latter combination was not significantly better than omeprazole alone (80%).¹¹⁷ This study is representative of maintenance trials of GERD, showing significantly better remission rates with PPI therapy than with H₂-antagonists or prokinetic regimens.

PPIs are also effective in the treatment of esophageal strictures, a well-known complication of erosive GERD. Management of strictures consists of endoscopic dilation and antisecretory therapy to heal esophagitis. Studies comparing PPI to H₂-antagonist therapy have shown that the former heals esophagitis more effectively and decreases the eventual number of esophageal dilations required to relieve dysphagia.^{118,119} Medical therapy in cases of Barrett's esophagus is aimed at healing the associated esophagitis. PPIs are effective in promoting healing, but do not appear to reduce the length of Barrett's segments. Interestingly, patients treated with PPIs in several studies did develop islands of squamous mucosa within the Barrett's segments.¹²⁰ However, to date, no studies have shown true regression of Barrett's esophagus or a decrease in the risk of esophageal malignancy with medical therapy. Similarly, antireflux surgery clearly heals esophagitis and relieves symptoms, but it does not produce regression of the Barrett's mucosa.¹²¹

The role of duodenogastric reflux of bile in the pathogenesis of GERD remains controversial. Vaezi and Richter¹²² found that acid and duodenogastric bile reflux commonly occurs simultaneously in patients with complicated and severe GERD. However, they also reported that esophageal mucosal injury as a result of bile acids is pH dependent. PPIs not only decrease gastric volume, thereby decreasing gastroesophageal reflux, but also increase intraluminal pH, resulting in precipitation of conjugated bile acids. Zhang et al.¹²³ recently demonstrated that dihydroxy bile acids, such as deoxycholate and chenodeoxycholate, may induce cyclooxygenase 2 transcription in human esophageal carcinoma cells, an effect that may explain their tumor-promoting effects. Whether bile acids promote the progression of Barrett's metaplasia to dysplasia has not yet been determined.

A recent study by Lagergren et al.¹²⁴ reported a strong etiologic relationship between adenocarcinoma of the esophagus and GERD, with the greatest risks correlating with more frequent, more severe, and longer-lasting reflux. They also reported that patients treated medically had a greater cancer risk than those who were not. It is highly unlikely that medical therapy itself increases the risk of esophageal adenocarcinoma. Nevertheless, while antireflux therapy is clearly indicated for the management of GERD, no studies to date have proven that either

medical or surgical treatment alters the natural history of Barrett's esophagus. The results of these studies thus emphasize the need for continued surveillance of patients with Barrett's esophagus despite maximal acid suppression with PPIs or surgical therapy. Fundoplication offers the theoretical advantage of decreasing both gastroesophageal and duodenogastric reflux, but many endoscopists have found Barrett's surveillance technically far more difficult in surgically treated individuals.

It has become increasingly evident in recent years that a number of tracheopulmonary and other extraesophageal symptoms may occur as a result of acid reflux. In reflux-induced asthma, airway reactivity may be caused by either the aspiration of refluxed gastric contents or by vagally mediated bronchoconstriction induced by the presence of acid in the esophagus. Previous studies have indicated that 34%–89% of patients with asthma have concomitant GERD. However, because GERD and asthma are such common entities, an etiologic relationship has been difficult to establish. An uncontrolled trial of 30 patients with asthma and GERD proven by pH monitoring conducted by Harding et al.¹²⁵ showed that a 3-month course of omeprazole led to symptom improvement or improved pulmonary function in 73% of subjects. In this study, most of the improvement was detected in a small group of individuals, suggesting that acid reflux may be the principal asthma trigger in a small, but as yet undefined, group of individuals. Unfortunately, no randomized, controlled studies evaluating the efficacy of antisecretory therapy for asthma have been performed to date. Although idiopathic hoarseness and other symptoms of chronic laryngitis have been associated with GERD in several small series, studies evaluating the precise etiologic relationship between otolaryngologic symptoms and GERD are likewise lacking in rigor. Interestingly, in studies that included pH monitoring of patients with laryngeal symptoms and GERD, a significantly higher incidence of proximal acid reflux was detected in patients with otolaryngologic symptoms, suggesting that direct acid exposure probably contributes to the otolaryngologic symptoms in these patients.¹²⁶ Trials of therapy in these patients are either small or uncontrolled, but they do suggest true benefit in patients treated with PPIs generally administered in 2 doses (before breakfast and before the evening meal).¹²⁷

Noncardiac chest pain (NCCP) refers to a syndrome of substernal chest pain in patients with no identifiable cardiac disease. Many individuals with this disorder appear to have an esophageal source for their symptoms, with GERD and esophageal dysmotility disorders accounting for the majority of cases in which an esophageal origin of the pain syndrome is identified. The history

alone does not satisfactorily distinguish between cardiac and esophageal etiologies of chest pain with sufficient accuracy, and classic anginal symptoms may occur with chest pain of esophageal origin. It is thus imperative to first exclude ischemic heart disease before embarking on a gastroenterological evaluation. Several studies, however, have shown that acid reflux is the most common cause of NCCP, accounting for 25%–50% of cases in several studies.¹²⁸ Once a cardiac etiology of chest pain has been excluded, an endoscopy is recommended to search for gastroduodenal ulcer, esophageal or gastric cancer, or esophagitis (infectious or reflux-related). If the endoscopy is unrevealing, nonerosive GERD may still be the etiology of chest pain, and an empirical trial of PPI therapy is recommended.^{129,130} Fass et al.¹³⁰ recently demonstrated the usefulness of such an empirical trial in determining the etiologic significance of GERD in such individuals. If symptoms persist despite 12 weeks of therapy, ambulatory pH monitoring while the patient is on therapy may be useful in assessing the adequacy of acid suppression and documentation of reflux episodes. This evaluation is often done in conjunction with esophageal manometry to identify any esophageal dysmotility that may be responsible for NCCP.

In general, it appears reasonable to recommend that patients with extraesophageal symptoms possibly related to GERD be given at least a 2–3-month empirical trial of PPI therapy, with doses administered before breakfast and before the evening meal.¹²⁹ If symptoms do improve, it can be surmised that the symptoms are probably acid related. If symptoms persist, a 24-hour esophageal dual-probe pH study should be performed to determine whether acid suppression has been achieved. If patients remain symptomatic despite adequate acid suppression, it may be assumed that symptoms are not caused by acid reflux, provided that therapy has been optimal for a sufficient period.

Recently, an association between long-term PPI use and atrophic gastritis was postulated. In a study by Kuipers et al.¹³¹ of patients with GERD treated either with antireflux surgery or omeprazole maintenance therapy, atrophic gastritis was detected after 5 years of treatment in 31% of PPI-treated patients who were *H. pylori* positive. During this same period, none of the patients treated surgically developed atrophic gastritis.¹³¹ Eissele et al.¹³² also reported that *H. pylori*-positive individuals treated with lansoprazole were at increased risk for the progression of fundic atrophy and the development of argyrophil cell hyperplasia. In this study,¹³² no patient developed dysplastic changes or carcinoid tumor formation, and atrophic changes worsened primarily during the first 2 years of therapy, with

little deterioration thereafter. Such observations led to concern over the possibility that long-term PPI therapy in *H. pylori*-infected patients might lead to an increased incidence of atrophic gastritis and possibly adenocarcinoma, and some recommendations were thus made to eradicate the organism in all patients before initiating extended courses of PPI therapy. However, similar studies in the United States and Scandinavia have not confirmed this increase in atrophic gastritis with PPI use, and an FDA summary based on available data determined that atrophic gastritis was not a significant complication of PPI therapy in *H. pylori*-infected patients.^{133,134} In addition, no studies have actually reported the development of dysplasia or gastric adenocarcinoma in humans, which generally occurs only after decades of atrophic gastritis and achlorhydria. Furthermore, recent studies have suggested that the antisecretory properties of PPIs may be enhanced in the setting of *H. pylori* infection¹³⁵ and that cagA-positive strains of *H. pylori* may actually protect individuals against the development of esophageal adenocarcinoma.¹³⁶ Finally, el-Serag and Sonnenberg¹³⁷ recently reported that, although a cause-and-effect relationship has not been clearly established, the incidence of *H. pylori* infection and ulcer disease appears to be inversely proportional to the incidence of GERD. Therefore, presently, routine eradication of *H. pylori* infection does not appear warranted in individuals with GERD in whom long-term PPI therapy is being contemplated. Long-term studies will be necessary to determine whether certain groups of individuals might benefit from antimicrobial treatment.

Antisecretory medication in the treatment of GERD. The question of which antisecretory drug regimen is optimal for the treatment of GERD has been the subject of ongoing debate. Advocates for both “step-down” (starting with a PPI and then converting a patient to long-term H₂-antagonist therapy) and “step-up” therapy present compelling arguments. With the availability of inexpensive generic H₂-antagonists, many physicians and particularly managed-care organizations have opted for the latter approach exclusively, and in doing so have often unnecessarily delayed effective therapy with PPIs, which at present are more costly. It is imperative that the overall direct costs of treating any disorder be considered, rather than merely the price of each individual tablet or capsule. The development of complications and long-term sequelae,¹²⁴ as well as patient satisfaction and work days lost, both of which contribute to the indirect costs associated with treating GERD, should be part of the equation in developing strategies for choosing antisecretory class. Complete symptom relief and mucosal healing should be the goal in all individuals with GERD.

Despite the unequivocal superiority of PPIs over H₂-receptor antagonists in both relieving symptoms and in healing esophagitis, the majority of individuals with acid reflux disease have mild-to-moderate, intermittent symptoms, usually in the absence of esophageal mucosal injury. Therefore, in many individuals, initial treatment with H₂-receptor antagonists may be effective in providing symptom relief. Another argument in favor of a “step-up” approach is the property of PPIs to produce rebound acid hypersecretion,¹³⁸ particularly in individuals not infected with *H. pylori*, a phenomenon that may render H₂-antagonists ineffective and mandate the continued use of a PPI. Also, as discussed previously, PPIs are not effective inhibitors of gastric acid secretion when given only “as needed,” and it is difficult to advocate continuous treatment with a PPI under such circumstances, unless it is the only regimen that provides satisfactory symptomatic improvement. In general, the treatment of GERD differs significantly from the treatment of gastroduodenal ulcer, in which “one dose (of medication) fits all.” Specific recommendations for the use of antisecretory medication in treating GERD vary significantly among individuals and clearly are dependent on the frequency and severity of the symptoms and the presence or absence of mucosal injury. Furthermore, in contrast to ulcer disease, in which maintenance therapy can usually be accomplished using a dose of medication lower than the one necessary for healing an active ulcer, the drug regimen used to initially heal esophagitis and control GERD symptoms is commonly the same one required to maintain an individual in remission. The final decision is one that each physician must make, often with input from individual patients. Figure 8 offers a suggested approach to the use of antisecretory medication in the treatment of GERD.

Stress-Related Erosive Syndrome

The treatment of established or presumed SRES involves the institution of nonpharmacologic medical principles applicable to the care of the critically ill patient at risk, including adequate and aggressive volume resuscitation,^{139–141} antimicrobial therapy (especially for intra-abdominal sources of sepsis),¹⁴² and optimal tissue oxygenation.¹⁴³ In addition, because luminal acid plays a dominant role in producing the multiple erosive lesions characteristic of the entity, alkalinization of the gastric lumen has historically comprised the mainstay form of prophylactic therapy in preventing GI hemorrhage associated with this entity.

Antacids. Several placebo-controlled trials have demonstrated the efficacy of antacids in significantly reducing the frequency of overt and clinically significant

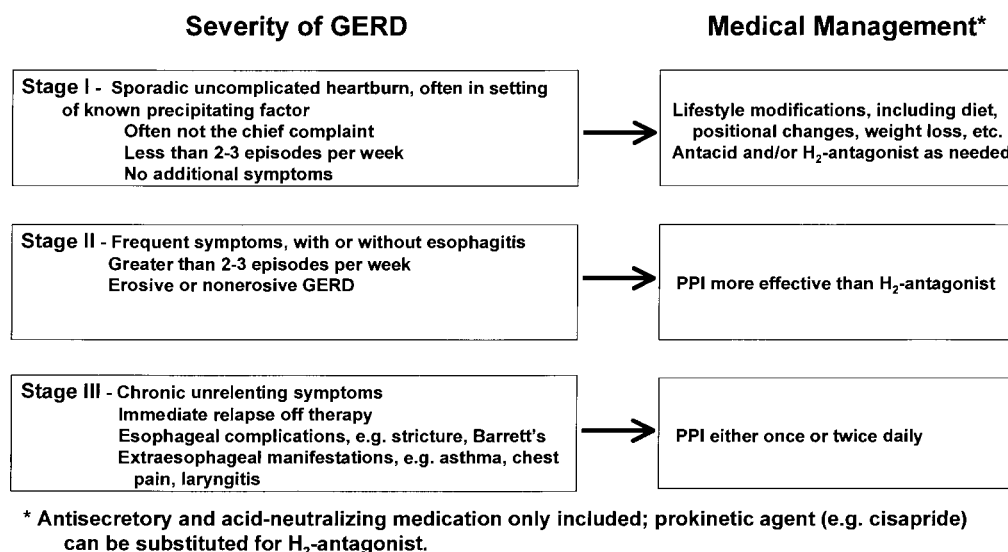


Figure 8. A suggested approach to the use of acid-neutralizing and antisecretory medication in the treatment of GERD of different severity.

GI bleeding from SRES.^{144,145} Antacids exert their beneficial effects by decreasing intragastric acidity through direct neutralization and by binding pepsin,¹⁴⁵ although other studies have postulated additional gastroprotective mechanisms.^{146,147} Aluminum-based compounds appear to increase mucus and bicarbonate production, increase gastric mucosal blood flow, bind potentially injurious agents like bile acids, and stimulate epithelial cell renewal.¹⁴⁵ The goal of acid neutralization is to increase the intragastric pH to 4 or greater to prevent the catalytic conversion of pepsinogen to its biologically active form, pepsin, and thereby reduce proteolytic activity in the gastric lumen. In addition, platelet aggregation normalizes above a pH of 5.9, which provides further protection against hemorrhage. Antacids are typically administered as 30–60-mL aliquots orally or via a nasogastric tube every 1–2 hours.^{148,149} The regimen requires close monitoring of intragastric pH and individual titration to maintain the intragastric pH above 4. In addition to diarrhea, which can be quite severe because of the volume of antacids needed to maintain the luminal pH above 4, the side effects of magnesium-containing antacids include alkalemia and hypermagnesemia, and aluminum-based antacids cause hypophosphatemia, constipation, and metabolic alkalosis, as well as potentially toxic plasma aluminum levels in patients with renal insufficiency.¹⁵⁰ Furthermore, all antacids can impair the systemic absorption of drugs, including antibiotics and H₂-antagonists.¹⁵¹

Histamine H₂-receptor antagonists. H₂-receptor antagonists have been shown unequivocally to reduce the incidence of overt and clinically significant SRES-associated hemorrhage when compared with untreated controls.^{145,152} A meta-analysis of 16 studies involving 2133 patients by Shuman et al.¹⁵³ showed no significant

difference in efficacy between antacids and H₂-receptor antagonists in preventing clinically significant hemorrhage caused by SRES. Moreover, both regimens were shown to be superior to placebo and were tolerated equally well. More recently, a meta-analysis by Tryba et al.¹⁴⁵ has suggested that H₂-blockers may be more effective than antacids in SRES prophylaxis. Cimetidine is typically administered intravenously by continuous infusion at doses of 37.5–100 mg/h, while ranitidine is dosed at 6.25–12.5 mg/h and famotidine at 1.7–2.1 mg/h. All can be administered with or without a loading dose,³⁷ although as discussed above, dose adjustments are necessary for individuals with impaired renal function (Table 2). Continuous H₂-receptor antagonist infusion appears to provide more stable acid suppression than intermittent administration.^{37,154–157} Currently, because of their efficacy and excellent safety profile, as well as ease of administration, H₂-receptor antagonists are generally preferred over antacids and PPIs in the prevention of SRES-associated GI hemorrhage. A potential problem with their use, however, might arise once a patient resumes feeding and a decision is made to continue antisecretory therapy, but to change to an oral PPI. Studies to examine this question have yet to be performed, but a reasonable suggestion would be to wait a period of 6–8 hours between stopping parenteral cimetidine and ranitidine and 10–12 hours after discontinuing famotidine before starting feeding and initiating therapy with a PPI.

PPIs. Some controversy exists regarding the role of PPIs in SRES prophylaxis. Despite a few small studies suggesting a beneficial effect,^{158,159} no large randomized, clinical trials have been performed to date to reliably assess the true benefit of these agents in preventing SRES-associated GI hemorrhage. Two recent studies in

mechanically ventilated ICU patients suggested that a simplified omeprazole suspension may not only prevent clinically significant SRES-induced hemorrhage but also is safe and cost-effective.^{160,161} However, the study designs were limited in scope, and patient numbers were small. Furthermore, omeprazole and other PPIs have an enteric coating that has been formulated to dissolve at an alkaline pH. The instillation of these granules through a nasogastric tube might disrupt this coating within the gastric lumen, which may cause acid-catalyzed conversion to its reactive species. Finally, it must be emphasized once again that PPIs are prodrugs, which are normally activated after systemic absorption in the highly acidic milieu of the secretory canaliculus of *activated* parietal cells.^{162,163} Activation occurs after a meal, and because individuals at risk for the development of SRES are generally fasting, these drugs would be significantly less active.¹⁶² Despite a prolonged biological half-life, the plasma half-life of PPIs is quite short (2–3 hours), and if administered intermittently, several doses would be required to achieve adequate inhibition of H^+, K^+ -ATPase. The initial dose of the PPI will only inhibit activated H^+, K^+ -ATPase present in the canalicular membrane, and as inactive enzyme is continuously recruited into the secretory canaliculus, acid secretion will resume after a short period of inhibition. Only pantoprazole is currently available in the United States as an intravenous preparation,¹⁶³ and although no studies examining this agent in the prophylaxis of SRES have been reported, the continuous infusion of this agent might be expected not only to adequately inhibit acid secretion, but also to allow a smooth transition to oral PPI therapy. Until these issues are resolved with the performance of well-designed, randomized, controlled trials, it seems that H_2 -receptor antagonists are preferred over the PPIs in preventing GI hemorrhage associated with SRES.

Inhibition of acid secretion and nosocomial pneumonia. The possibility of an increased risk of nosocomial pneumonia has been suggested as a complication of antisecretory therapy for SRES. This notion stemmed from studies showing that gastric bacterial colonization can occur after only a few days of an alkaline intragastric milieu ($pH > 4$). In addition, a higher gastric pH correlates directly with logarithmic increases in the concentration of gram-negative organisms in the gastric aspirate.¹⁶⁴ In a large study of mechanically ventilated patients at risk for the development of SRES, Driks et al.¹⁶⁵ reported a pneumonia rate of 12% with sucralfate, a basic nonabsorbable aluminum salt of sucrose octasulfate, compared with a 23% incidence in the group receiving antisecretory medication consisting of cimetidine with or without antacids. Upon stratification,

antacids were associated with a 23% incidence of pneumonia, while only 5.9% of the H_2 -receptor antagonist group (lower than those receiving sucralfate) developed pneumonia, implicating antacids, and not H_2 -blockers, as the culprit. Antacids increase gastric volume and thereby might increase the potential for aspiration, while the gastric volume of patients on antisecretory agents is clearly diminished.¹⁶⁵ A more recent meta-analysis of trials by Cook et al.¹⁶⁶ examined drug class-specific rates of nosocomial pneumonia and concluded that sucralfate causes significantly less pneumonia than H_2 -antagonists. Unfortunately, in some studies, sucralfate was somewhat less effective than alkalinizing agents in preventing SRES-associated GI hemorrhage.^{165,167–170}

Taking all these issues into consideration, it would appear that the positive attributes of H_2 -receptor antagonists outweigh the risk of nosocomial pneumonia associated with their use. Their intravenous administration obviates the need for a nasogastric tube, which is often necessary when administering antacids or a sucralfate “slurry,” and not only causes discomfort, but also may serve as a conduit for the migration of bacteria from the stomach to the pharynx.¹⁶⁵ Although the use of a PPI, like pantoprazole, by primed continuous infusion offers a theoretical advantage in the transition from intravenous to oral therapy, any recommendation regarding their use in preventing GI hemorrhage associated with SRES must await formal trials evaluating their efficacy and safety.

GI Hemorrhage

Although a few reports have suggested benefit associated with the use of antisecretory agents in the control of nonvariceal GI hemorrhage,^{171,172} most have found these agents to be ineffective.^{173,174} The rationale for the use of antisecretory agents stems from the notion that at least two-thirds of cases of GI bleeding are associated with an acid-related disorder, such as gastroduodenal ulcer, gastritis, and esophagitis. In addition, after initial clot formation, the avoidance of clot lysis may reduce recurrent hemorrhage. Previous studies have shown that both clot formation and the prevention of clot lysis occur more effectively at higher pH levels.^{175,176} The only antisecretory agents that have been examined to any extent are the H_2 -receptor antagonists and PPIs. Somatostatin also inhibits acid secretion by several mechanisms, and although this regulatory peptide and its analogues have been evaluated in the treatment of both variceal and nonvariceal GI hemorrhage, its principal effect appears to be a reduction in splanchnic/portal blood flow.

H_2 -receptor antagonists. No single study has convincingly demonstrated an overall benefit of H_2 -antagonists in the cessation of acute upper GI hemor-

rhage or in the prevention of recurrent bleeding. However, Collins and Langman¹⁷¹ reported a meta-analysis of 27 randomized, controlled trials involving more than over 2500 individuals with upper GI bleeding who had been treated with H₂-antagonists. The odds ratio for a beneficial effect of H₂-blockers on the cessation of bleeding, the need for surgical intervention, and mortality were 0.89 ($P = \text{NS}$), 0.78 ($P = 0.05$), and 0.70 ($P = 0.02$), respectively. The authors of this study concluded that therapy with H₂-antagonists "... appears to be moderately promising, but... still needs to be assessed reliably. To detect... effect reliably might require randomization of 10,000 patients or more."¹⁷¹

PPIs. The recent availability of more potent inhibitors of gastric acid secretion has renewed interest in the use of such agents in controlling upper GI hemorrhage. In a double-blind, placebo-controlled trial, Daneshmend et al.¹⁷⁷ examined the effects of omeprazole in 1147 patients with nonvariceal upper GI hemorrhage. Omeprazole was given intravenously on the first day, followed by 80 mg daily for the next 72 hours. No significant differences were detected between the omeprazole and placebo groups with regard to control of hemorrhage, transfusion requirements, or the need for surgical intervention. In a second study by Khuroo et al.,¹⁷² 220 patients with bleeding duodenal, gastric, or stomal ulcers were randomized to 40 mg omeprazole or placebo orally every 12 hours for 5 days. Bleeding continued in 10.9% and 36.4% of the patients receiving omeprazole and placebo, respectively, and 29.1% and 70.9% of those receiving omeprazole and placebo, respectively, required blood transfusions (both $P < 0.001$). While mortality was not reduced significantly in the omeprazole group, a trend favoring the PPI was observed (1.8% vs. 5.5%). It is important to note that endoscopic therapy, usually the modality of choice for bleeding ulcers, was not employed at all during the course of this trial.¹⁷² Furthermore, despite benefit in this study, PPIs are activated after systemic absorption, which occurs following a meal, and because individuals with actively bleeding ulcers are usually fasting, these drugs would be significantly less active unless used frequently at higher doses or by continuous intravenous infusion.

More recently, Lin et al.¹⁷⁸ compared the effects of cimetidine and omeprazole, both administered by primed continuous intravenous infusion, in 100 patients with bleeding ulcers controlled initially by endoscopy, a contemporary approach more analogous to the current therapy of this clinical scenario in the United States. They found that omeprazole (160 mg/day) was more effective than cimetidine (1200 mg/day) in maintaining the intragastric pH above 6.0 and in preventing recurrent

ulcer-related hemorrhage (4% vs. 24%, $P = 0.004$). Therefore, because of the safety of antisecretory agents and the frequency of acid-related GI bleeding lesions, it is not unreasonable to treat individuals with hemorrhage from an upper GI source initially with either an H₂-receptor antagonist or a PPI, preferably administered via the intravenous route, until diagnostic and therapeutic endoscopy can be performed. If an ulcer is detected at endoscopy, antisecretory drugs should be instituted after injection, thermal coagulation, or electrocoagulation to treat the active ulcer and possibly to prevent rebleeding.^{178,179}

Nonulcer Dyspepsia

An exhaustive review of an approach to the patient with nonulcer dyspepsia is beyond the scope of this manuscript and has been the subject of a recent review and position statement in *Gastroenterology*.^{180,181} Moreover, the role of *H. pylori* infection in the etiology of dyspepsia, if any,^{182,183} is discussed elsewhere in this Supplement. In general, patients with GERD and those with a biliary etiology, most of whom can be identified by obtaining a careful history, should ideally be removed from the category of nonulcer dyspepsia. Individuals with dyspeptic symptoms who fit specific criteria, which include age <45 and the absence of any alarm symptoms, may be treated empirically with either antisecretory agents or prokinetic medication. The latter should be used if features suggestive of a motility disturbance are evident, such as concomitant features of irritable bowel syndrome, abdominal distention, eructations, or detection of a psychological disturbance. In most other settings, including dyspepsia associated with the use of NSAIDs,¹⁶ antisecretory medications are often used and have been reported in some studies to be helpful in relieving symptoms.^{180,181,184} However, with the exception of NSAID-related dyspepsia,¹⁶ universal and unequivocal benefit of antisecretory agents in the symptomatic treat-

Table 6. Recommendations for Antisecretory Drug Treatment of Nonulcer Dyspepsia

H ₂ -receptor antagonists
Cimetidine 400 mg twice/day
Ranitidine/nizatidine 150 mg twice/day
Famotidine 20 mg twice/day
Therapy should be individualized to fit patient requirements; often effective when administered between breakfast and lunch, and between the evening meal and bedtime
PPIs
Omeprazole 20 mg daily
Lansoprazole 30 mg daily
Rabeprazole 20 mg daily
Pantoprazole 40 mg daily
All administered daily before breakfast; second dose, if necessary, should be given before evening meal

ment of dyspepsia has not been demonstrated.^{185,186} Moreover, it is important to avoid introducing long-term drug use in individuals with “functional dyspepsia,” particularly because of the considerable benefit of placebo in such individuals.¹⁸⁶ When employed, the initial doses of medication, whether H₂-antagonist or PPI, should generally be low (Table 6), and dosing should be flexible and optimized to meet the individual needs of each individual. If used on an “on-demand” basis, H₂-blockers offer an advantage over PPIs because of their relatively fast onset of action and, as discussed previously, the length of time necessary to achieve steady-state concentrations when using the latter.

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