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Post-graduate Excellence Program on

# ACID PEPTIC DISORDERS & IBS

**Course Director**

Dr. Robert C. Lowe, M.D.  
Associate Professor of Medicine  
Boston University School of Medicine,  
Boston, MA

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# Course information

## Program overview

Gastroenterology is probably the one medical domain with distinct indistinctness. In practice, this is well evident with wide influx of patients with complaints such as fullness, discomfort, bloating, heartburn, belching, nausea, vomiting, and/or pain. In this regard, despite major advances in the domain, both in identification and characterization of different related conditions according to various criteria (such as the ROME criteria), facilitating a multimodal approach for each entity, the complexity of clinical gastroenterology still prevails. Most people present with complaints, which often put the attending clinician in a dilemma concerning their cause, i.e., if the symptoms are because of an underlying "organic cause" or "functional" in origin. This invariably delineates the need of having continual knowledge about varied facts and concepts related to the practice of gastroenterology.

This certificate program is an attempt to update clinicians regarding two characteristic gastrointestinal presentations: "Acid peptic disorders", which include Peptic ulcer disease (PUD) and Gastroesophageal reflux disease (GERD) in particular; and the "Irritable bowel syndrome (IBS)".

The program is available in online format, and starts with explaining in detail the finer points about the conditions, their pathogenesis, and identification based on clinical presentations, and pertinent management approaches.

## Program objectives

Once completing these activities, participants will be better able to:

1. Identify different acid-peptic disorders, and their origin and identification in practice
2. Recognize different concepts related to the pathogenesis, presentation and identification of IBS
3. Identify characteristic differential approaches related to management of patients presenting with these two clinical entities as based on evidence-based information.

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Dr. Robert C. Lowe, M.D.

Associate Professor of Medicine

Boston University School of Medicine, Boston, MA

## Method of participation

- Study all parts of the educational activity available in online format
- Submit the posttest questions with answers, evaluation and request for certificate of participation forms
- A certificate of participation will be issued by Boston University School of Medicine upon completing the evaluation and the posttest with a score of 60% or better.

## Course Code

E.PPDiplomaGI13

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# CASE STUDY

## History

A 42 year-old man with a history of osteoarthritis and HTN presents to his physician with a 6 week history of abdominal pain. He describes it as epigastric, with a "burning" or "aching" quality, with no radiation to the chest or back. It occurs nearly every day, and can wake him at night on occasion. He has had some relief with over-the-counter antacids, but he notes no exacerbation with meals or with changes in position. He has had no change in his appetite and no weight loss. He reports daily solid bowel movements that are brown in color.

His past history is remarkable for osteoarthritis of the knees, and HTN. His medications include HCTZ daily and ibuprofen PRN for pain. He does not smoke, he drinks 1-2 glasses of wine per night with dinner, and he uses no illicit drugs. He owns a sporting goods store, is married with 3 children. Family history is non-contributory. He is originally from the Dominican Republic, but immigrated to the US 20 years ago.

## Physical Examination

- T 98.3; P 75; BP 130/72; RR 14
- Anicteric sclerae, normal oropharynx
- Chest clear to auscultation
- Cardiac examination unremarkable
- Abdominal exam reveals positive bowel sounds, a soft, non-distended abdomen, mildly tender in the epigastrium with no masses appreciated. There is no hepatosplenomegaly.
- Extremities reveal no clubbing, cyanosis, or edema
- Skin examination unremarkable.



IMAGE 1. DUODENAL ULCER

## Laboratories

- WBC 7.5; HCT 31.4; MCV 70; PLT 450
- LFTs all normal
- Upper endoscopy was performed, revealing a 1.5 cm ulcer in the duodenal bulb, with no stigmata of recent hemorrhage (Image 1).

## Questions

1. This patient required upper endoscopy for evaluation of dyspeptic symptoms for which of the following reasons?
  - a. Male gender
  - b. Age > 40
  - c. Presence of anemia
  - d. Nocturnal symptoms
  - e. 6-week duration of symptoms
2. If this patient's ulcer disease were due to Zollinger-Ellison Syndrome, which of the following would most likely be present?
  - a. A family history of peptic ulcers
  - b. A low serum gastrin level
  - c. Episodic hypoglycemia
  - d. A history of chronic watery diarrhea
  - e. Jaundice
3. If this ulcer is due to *H. pylori* infection, which of the following statements regarding therapy is true?
  - a. Antibiotic therapy for one month is recommended to eradicate the bacterium
  - b. Regimens including clindamycin are the most effective in treating this infection
  - c. Antibiotics must be given in liquid formulations to ensure coating of the gastric mucosa
  - d. Cure rates are 50-60%
  - e. Therapy must be tailored depending upon local antibiotic resistance patterns
4. If this patient is found to be *H. pylori* negative, and he wishes to remain on NSAID medications, what should be recommended?
  - a. Initiation of prostaglandin analogue therapy
  - b. Initiation of chronic PPI therapy
  - c. NSAIDs must be discontinued to prevent ulcer recurrence
  - d. Initiation of chronic H2 blocker therapy
  - e. Surveillance EGD yearly

# ACID PEPTIC DISORDERS

## An Introduction

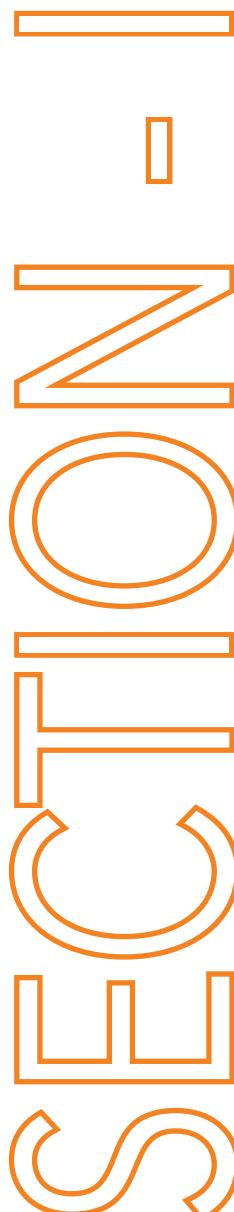
### Course Director

Dr. Robert C. Lowe, M.D.

Associate Professor of Medicine

Boston University School of Medicine,

Boston, MA



### THE ORIGIN OF ACID PEPTIC DISEASES

Comparative anatomy and physiology studies have indicated that gastric acid secretion developed during the evolution of vertebrates approximately 350 million years ago.<sup>1</sup> Unfortunately, gastric acid eventually became pathogenic in many gastrointestinal disorders, and is still a matter of concern both in hypo- and hyper-secretory states, with the latter in particular.<sup>2</sup> In effect, acid-peptic disorders have emerged worldwide, and have been increasingly on rise in today's era of globalization.<sup>3</sup>

Importantly, this acid secretion plays a significant role in the pathophysiology of acid-related disorders, such as peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD), the two most common acid peptic diseases, and also contributes to entities such as drug [non-steroidal anti-inflammatory drug (NSAID)]-induced or stress-related gastrointestinal lesions.<sup>4,5</sup>

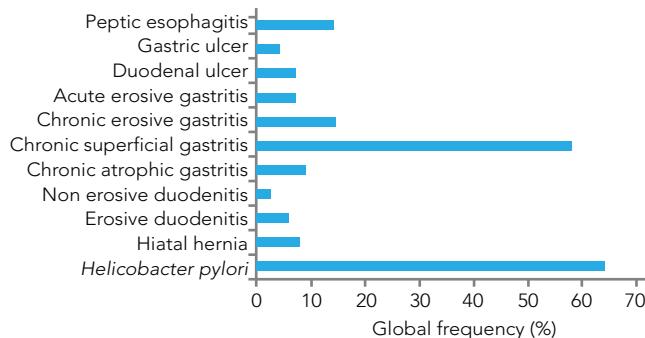
### Frequency of acid peptic disorders at the first level endoscopic center – epidemiologic correlates

The manifestations of acid peptic diseases are frequently observed at the first level endoscopic center and include a variety of lesions that can occur from the esophagus to the duodenum, with rare occurrences in the jejunum and ileum. A retrospective, descriptive and analytical study of a series of patients [62.3% women, 37.7% men (mean  $44.0 \pm 16$  years)] described the epidemiological characteristics of individuals suffering from acid peptic disease at a first level endoscopic diagnostic center between 1993 and 2007. Important endoscopic findings in these patients included peptic esophagitis in 14.1%, gastric ulcer in 4.1%, and duodenal ulcer in 7.0% (Figure 1).<sup>6</sup> Only the frequency of duodenal acid peptic disease had decreased significantly in the period observed, which was associated with increased utilization of proton pump inhibitors (PPIs).

### The importance of acid-related symptom patterns in practice

Probably the most important concern in general gastroenterology practice is the differentiation of the different causes of difficult digestion (i.e., dyspepsia), often the prime presentation in gastroenterology clinics. The major issue is to determine whether symptoms are due to an organic cause, such as GERD or PUD, or due to non-ulcer (functional) dyspepsia, given that symptoms alone cannot separate adequately a functional from an organic cause of dyspepsia. In such

**FIGURE 1.** Frequency of some endoscopic diagnostics in a first level diagnostic endoscopy center



Source: Reference 6.

a setting, while heartburn and regurgitation are classic symptoms of GERD, duodenal and gastric ulcers are more often associated with epigastric pain – importantly, the relationship between gastric acid and the presence of symptoms correlates well in GERD and duodenal ulcer, but less so in gastric ulcer and non-esophageal reflux disease (NERD). Yet, in all these disorders, gastric acid, the proposed main culprit, is considered a key pathogenic element and a major prerequisite, making acid suppression central to therapy.<sup>7,8</sup>

Nevertheless, besides the direct consequences of gastric acid secretion, a pivotal development in understanding acid-peptic disorders has been the recognition of the role of *Helicobacter pylori* (*H. pylori*) in the pathophysiology of PUD, chronic gastritis, and gastric malignancy. However, the evolution of our understanding continues as medicine is continually challenged to treating iatrogenic conditions brought on by ulcerogenic anti-inflammatory drugs and other attackers, which makes the characterization of these clinical entities important.<sup>9</sup>

## A BRIEF ABOUT GASTRIC PATHOPHYSIOLOGY AND SECRETION

Before moving on to the discrete pathologic phenomenon of acid peptic disorders (discussed in later sections), let us review the physiologic concept of gastric acid secretion. The past several years have seen significant advances in our understanding of the molecular mechanisms underlying stomach innervation, the differentiation of gastric epithelial cell lineages, and their respective hormones/factors, all of which influence acid production.

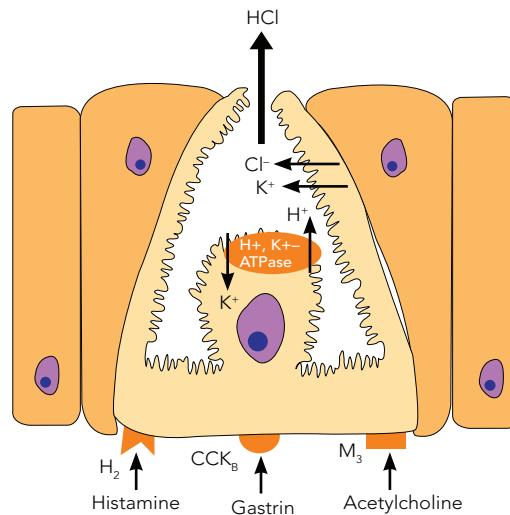
Gastric acid production is a tightly controlled physiological process that involves neural and hormonal mechanisms, and the input of several epithelial cell types via a paracrine route<sup>10</sup>; H<sup>+</sup> is secreted by the oxytic

parietal cells, with its secretion being regulated by several endocrine, neurocrine and paracrine mechanisms.<sup>11</sup> Acetylcholine, gastrin, and histamine are the key players directly stimulating acid secretion by binding to specific receptors on parietal cells (Figure 2)<sup>8,12</sup>; a plethora of other mediators and hormones affect parietal cell function, either directly or indirectly via stimulation of enterochromaffin-like (ECL) cells or gastrin-producing G-cells.

Most pertinent to this acid physiology is the role of the gastric H<sup>+</sup>,K<sup>+</sup>-ATPase that pumps H<sup>+</sup> into the lumen and takes up K<sup>+</sup> in parallel (Figure 2).<sup>8,12</sup> In addition, the acid-producing parietal cells display luminal KCNE2/KCNQ1 K<sup>+</sup> channels that play a pivotal role in replenishing K<sup>+</sup> in the luminal fluid. Stimulation of the parietal cell occurs via the acetylcholine (M<sub>3</sub>), gastrin (CCK<sub>B</sub>) and/or histamine (H<sub>2</sub>) receptors on the basolateral membrane via second messengers, resulting in movement of H<sup>+</sup>,K<sup>+</sup>-ATPase to the apical membrane of the cell where it can exchange H<sup>+</sup> for K<sup>+</sup>. Concurrently, chloride ions (Cl<sup>-</sup>) enter the secretory canalliculi from the cytoplasm through passive transport, resulting in the secretion of HCl (Figure 2).<sup>8</sup>

Amino acids stimulate parietal cells acid secretion indirectly via allosteric activation of the Ca<sup>2+</sup>-sensing receptor on G-cells, which induces gastrin release, or directly by activating Ca<sup>2+</sup>-sensing receptors located on parietal cells. Moreover, amino acids taken up through L-amino acid transporters can stimulate acid secretion.<sup>12</sup> In addition, nutrients within the intestine, primarily lipids and protein, induce the release of peptide hormones such as cholecystokinin, secretin, neuropeptides, and glucagon-like peptide, which may act in unison to inhibit the acid secretion and maintain the acid homeostasis.

**FIGURE 2.** Schematic representation of acid secreting parietal cell



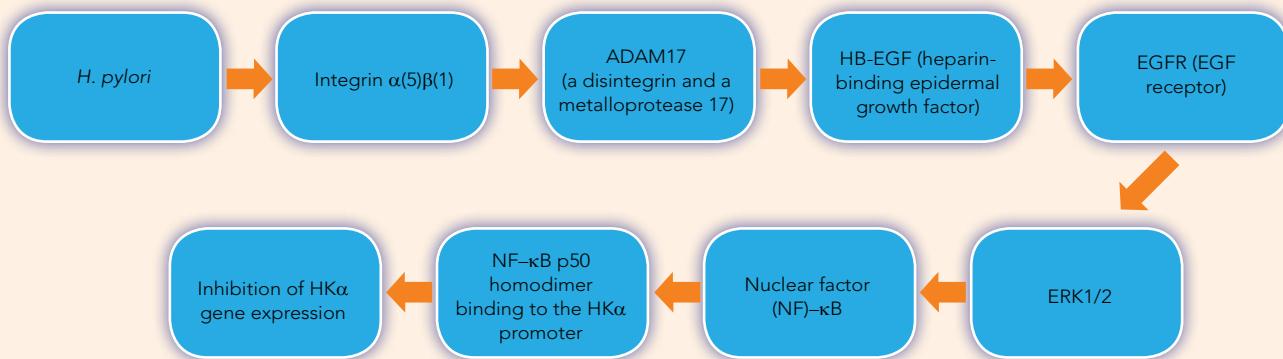
Source: References 8,12.

### How does *H. pylori* infection affect gastric acid secretion?

*H. pylori*, the primary cause of gastritis and PUD, is known to infect greater than 50% of the world's population.<sup>(i)</sup> Infection of the human stomach mucosa by *H. pylori* induces strong inflammatory responses, and a transitory hypochlorhydria. In vitro, *H. pylori* infection of gastric biopsies or cultured gastric epithelial cells was found to repress the activity of endogenous or transfected promoter of the  $\alpha$ -subunit (HK $\alpha$ ) of gastric H $+$ ,K $+$ -ATPase, the parietal cell enzyme mediating acid secretion.<sup>(ii)</sup>

In this regard, some mechanistic details of *H. pylori*-mediated repression of HK $\alpha$  and ensuing hypochlorhydria have been recently elucidated, which suggest that *H. pylori* inhibits HK $\alpha$  gene expression by pathway mediating NF- $\kappa$ B p50 homodimer binding to the HK $\alpha$  promoter (see figure below).

#### Proposed pathway for *H. pylori*-mediated repression of HK $\alpha$



*H. pylori* strains expressing a type IV secretion system (T4SS) encoded by the cag pathogenicity island upregulate the transcription factor NF- $\kappa$ B. CagL, a T4SS component of the bacterial pilus, binds to the integrin  $\alpha(5)\beta(1)$  to mediate translocation of virulence factors into the host cell and initiate signaling. During acute *H. pylori* infection, CagL dissociates ADAM 17 from the integrin  $\alpha(5)\beta(1)$  complex and stimulates ADAM17-dependent release of HB-EGF, EGFR stimulation, ERK1/2 kinase activation, and NF- $\kappa$ B-mediated repression of HK $\alpha$ . This leads to a novel pathogen-dependent mechanism of H $+$ ,K $+$ -ATPase inhibition.

#### Source:

- (i) Matthews GM, Butler RN. *Helicobacter*. 2005;10(4):298-306.
- (ii) Smolka AJ, Backert S. *J Gastroenterol*. 2012;47(6):609-18.

**Role of ghrelin:** During meal ingestion, gastrin provides an important physiological stimulus for acid secretion, primarily by inducing the release of histamine from ECL cells<sup>11,13</sup>; together, ghrelin, a growth hormone-releasing peptide, and orexin, may also function as stimulatory hormones. Ghrelin is also known to stimulate gastric motility, and, prior studies have found the action of ghrelin on acid secretion to be comparable to that of histamine and gastrin. The mechanism for the action of ghrelin on acid secretion may involve vagal neural activity and Yakabi and colleagues<sup>14</sup> have indicated that at molecular level histamine may mediate the action of ghrelin on acid secretion. Furthermore, a synergistic action of gastrin and ghrelin on gastric acid secretion is suggested. Thus, while gastrin has important roles in postprandial secretion of gastric acid, ghrelin may be related to acid secretion during fasting periods or at night.

### Importance of enterochromaffin-like cell in acid physiology

ECL cell activation is an important physiological pathway in the regulation of gastric acid secretion, being influenced by both activating and inhibiting stimuli. Long-term hypergastrinemia will induce ECL cell hyperplasia and may promote the formation of carcinoid tumors in some species; long-term potent acid inhibition in patients with acid-related disorders evokes a marked increase in plasma gastrin levels, leading to enlargement of oxytic mucosa with ECL cell hyperplasia. As a result, the induction of ECL cell hyperplasia and carcinoid tumors has been a topic of concern, though it appears to be a very low risk in primates and humans. Additionally, the activation of ECL cells also induces another clinical concern, i.e., rebound acid hypersecretion after acid inhibition therapy is discontinued.<sup>11</sup> Therefore, it is

important that clinicians be aware of important clinical safety issues related to the dose and duration of potent inhibitors of acid secretion.

### Gastric hyperalgesia and nociception – afferent signaling of gastric acid challenge

Vagal afferent pathways are suggested to play a key role in gastric chemonociception – endogenous acid modulates the sensory gain of acid-sensitive vagal afferents, and thus gastric acid, acting as a noxious stimulus, is a factor in the pain associated with peptic ulcer and other acid-related disorders such as GERD and gastritis.<sup>15</sup> Additionally, the finding that exposure to pro-inflammatory cytokines and the induction of experimental gastritis or gastric ulceration sensitizes vagal afferent pathways to gastric acid further implicates these neurons in gastric nociception.

## DIAGNOSIS IN GENERAL

Patients consulting for upper gastrointestinal symptoms present in many different ways, thus confounding diagnosis and management. In such a setting, regardless of the presenting symptoms, the physician must determine if there are any alarm features; though these have a low positive predictive value (PPV) for malignancy, all patients with these features should undergo prompt upper gastrointestinal endoscopy. A detailed medication history should be ascertained, with particular attention to compounds containing NSAIDs, both non-selective and COX-2 selective.<sup>16</sup>

While it is important to ascertain whether the symptom pattern suggests GERD, it should be recognized that dominant heartburn may be of limited value in some cases. However, if reflux disease is strongly suspected, and there are no alarm features, an empirical trial of a PPI should be given.<sup>16,17</sup>

### Methods of measuring gastric acid secretion

Numerous methods have been evaluated in the past in an attempt to measure gastric acidity, in order to study the role of gastric acid in gastrointestinal diseases and to evaluate the effects of acid suppressing drugs. These methods for measuring gastric acid include both invasive and non-invasive techniques (Table 1).<sup>18</sup> While invasive tube tests are uncomfortable and time-consuming, most of the non-invasive methods are at best semi-quantitative and more useful in detecting low or absent acid secretion. Overall, the decision to involve one of these methods, if at all required, should follow clinical discretion on a case-to-case basis.

### The aging gut – why are acid-related disorders particularly relevant in the elderly?

It has been noted that GERD and peptic ulcer become more common and more severe with the advancing age. Aging leads to a variety of physiologic changes in the oropharynx, esophagus, and stomach that increase the risk for esophageal and gastrointestinal disorders, having an impact on both prevalence and intensity of the upper gastrointestinal tract diseases. In addition, older individuals tend to have a higher prevalence of comorbid factors, such as *H. pylori* infection, smoking, the presence of other diseases, or use of medications (such as, NSAIDs, bisphosphonates) that increase their risk for acid-related disorders. Given these physiologic and comorbid factors, the elderly are at higher risk for GERD, drug-induced esophagitis, PUD, and complications related to the use of NSAIDs.<sup>(i), (ii)</sup>

Unfortunately, in the elderly patient with these disorders, symptom presentation may be subtle or atypical, resulting in a delayed diagnosis. Thus, endoscopy is the "gold standard" for the identification of mucosal disease, and should be performed in all patients with "new-onset" or persistent symptoms who are > 45 years of age, in addition to being indicated in individuals of any age who present with alarm symptoms, such as weight loss, vomiting, anemia, dysphagia, or evidence of gastrointestinal bleeding.

Generally, the treatment of older individuals with peptic ulcer or GERD and its complications is similar to that of younger individuals.<sup>(i)</sup> PPIs are the mainstay of therapy for symptom relief, healing of erosive esophagitis, resolution of peptic ulceration, reduction of the risk for NSAID-induced mucosal damage, and prevention of disease relapses. Together, the high prevalence of *H. pylori* infection in the elderly, with its role in the occurrence of gastric ulcers, gastric precancerous lesions, and gastric cancer, make diagnosis and eradication of *H. pylori* important in this population.

#### Source:

- (i) Franceschi M, Di Mario F, Leandro G, et al. *Best Pract Res Clin Gastroenterol.* 2009;23(6):839-48.
- (ii) Greenwald DA. *Am J Med.* 2004;117 Suppl 5A:8S-13S.

## TREATMENT IN GENERAL – THE EMPIRIC APPROACH TO INITIAL THERAPY

An integrative approach to therapeutic management invariably offers patients the best opportunity for resolution of disease and symptoms.<sup>19</sup> Pertinent pharmacologic approaches to decreasing acid exposure could include trying to neutralize secreted acid via antacids, prevent

**TABLE 1.** Methods for measuring gastric acid

Type of test	In use in clinical practice	Quantitative measure of gastric acid secretion
<b>Invasive methods</b>		
Conventional aspiration tests		
Test meals	5	3
Augmented histamine test	5	3
Intragastric pH measurements	3	5; gives a measure of gastric pH
<b>Endoscopic methods</b>		
EGT	3	3
CRT and modified CRT	5	5
<b>Non-invasive methods</b>		
Breath analysis including the hydrogen breath test and calcium carbonate breath test	5	3 (the calcium carbonate breath test)
Serum pepsinogens assay	3 (mostly as a screening test for gastric malignancy)	5
Scintigraphy and applied potential tomographic techniques	5	5
Alkaline tide	5	5
Dye tests (urinary and serum)	No longer used	5
Heidelberg capsule	Still used; but in a more technically superior version	5

EGT - Endoscopic Gastrin test; CRT - Congo Red Test; 5 – No; 3 – Yes.

Source: Reference 18.

stimulation of the parietal cell, improve mucosal defences, and, most importantly, to block the functioning of the proton pump.<sup>20</sup> Symptom relief after control of gastric acid secretion is one of the key goals of treatment, and this in fact has been the cornerstone of therapy in the successful management of all gastric acid-related disorders.<sup>7</sup>

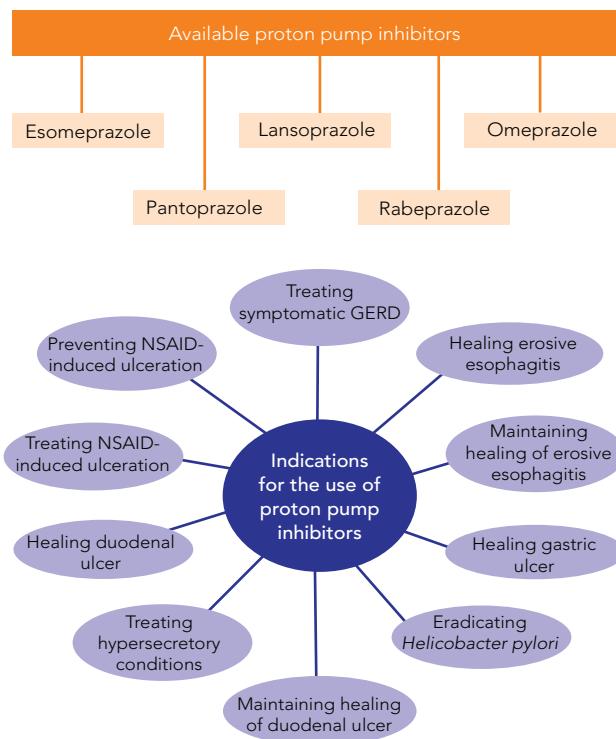
Agents targeting the histamine H2 receptor were first identified in the 1970s, followed by the development of irreversible inhibitors of the parietal cell hydrogen-potassium ATPase (the PPIs), which inhibit acid secretion much more effectively.<sup>21,22</sup> The proton pump inhibitors, with their profound, prolonged effect on acid production, consequent to inhibiting the final step of acid secretion, are potent acid inhibitors, and are considered the first-choice therapy for these disorders, being widely used these days (Figure 3).<sup>3,4,23,24</sup> In fact, they are the most effective drugs to treat all grades of GERD and PUD<sup>8</sup>, and are safe to use long-term in persons in whom there is a clear need for the maintenance of extensive acid inhibition.<sup>25</sup>

## PPIs versus H2-antagonists

PPIs, compared with H2-antagonists, have documented efficacy of a more effective relief of symptoms and healing, and exhibit a sophisticated mechanism of action.<sup>26,27</sup> Their superiority over the histamine H2 receptor antagonists is clear in moderate and severe esophagitis and in patients with persistent or severe symptoms related to GERD, and an associated benefit is the improvement of the quality of life obtained with this potent gastric acid inhibition profile.<sup>28</sup> Patients with milder symptoms of GERD may benefit from H2-antagonist therapy, but if symptoms persist, a PPI should be started.

## Within class PPIs selection – matter of choice?

Within class, PPI selection should involve the awareness of issues related to the drug class.<sup>2</sup> As treatment efficacy strongly correlates with degree and duration of acid

**FIGURE 3.** PPIs in practice

Source: Reference 24.

suppression within the 24-hour period and with total duration of therapy; all PPIs are highly effective for the healing of ulcers and erosive esophagitis. However, despite them having closely similar mechanisms of action, important pharmacological differences exist, which can significantly affect certain aspects of their clinical efficacy. For instance, rabeprazole's rapid activation over a wide pH range may explain for its early onset of effective acid inhibition compared with other PPIs such as omeprazole, lansoprazole and pantoprazole.<sup>29</sup>

Likewise, even as esomeprazole is also a potent inhibitor of gastric acid at steady state, rabeprazole is thought to provide enhanced first-day acid suppression compared with esomeprazole. This is consistent with the hypothesis that first-day antisecretory efficacy should produce faster symptom relief, as supported by clinical data. Besides, drugs with pharmacological profiles that include both rapid onset and potent anti-secretory effects should help control healthcare costs by reducing the need for otherwise commonly used twice-daily PPI administration. This again can help ensure patient acceptance of therapy and aid in patient compliance.<sup>7</sup>

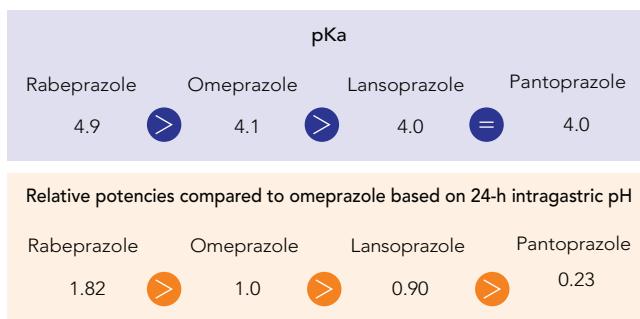
### Rabeprazole – a distinct PPI for acid peptic disorders

Rabeprazole is a potent and irreversible inhibitor of H<sup>+</sup>, K<sup>+</sup>-ATPase gastric pump, indicated for the treatment of almost all conditions requiring a reduction of gastric acid secretion, such as erosive or ulcerative GERD, NERD, duodenal and gastric ulcers, and pathological hypersecretory conditions including Zollinger-Ellison syndrome (ZES); and for the eradication of *H. pylori* in combination with antibiotics.<sup>30,31</sup> Besides, some success in the treatment of extraesophageal manifestations of GERD, such as asthma and chronic laryngitis, has also been achieved with rabeprazole.<sup>32</sup>

Of note, the drug, with a high pKa of approximately 5.0 ([Figure 4]<sup>31</sup>], can be activated at a higher pH than other PPIs, and this possibly results in a faster onset of action.<sup>32</sup> Like this, rabeprazole was found to be both rapid and effective in relieving heartburn on day 1 of therapy and improved other GERD-related symptoms including regurgitation, belching, bloating, early satiety and nausea.<sup>32</sup>

Importantly, the pronounced acid suppression achieved with rabeprazole from the first administration is maintained with repeated use – a finding that potentially translates into faster onset of symptom relief for patients; this may be particularly suitable when the indication is for the on-demand long-term maintenance of GERD. Besides, its predominantly non-enzymatic metabolism suggests that rabeprazole is less influenced by genetic polymorphisms of the CYP2C19, which others PPIs are dependent on, and has a lower potential for drug-drug interactions.<sup>30,33</sup>

Furthermore, another finding to facilitate the more widespread use of rabeprazole in acid peptic disorders could be the fact related to high association of *H. pylori* in these disorders, whereby, consistent with other PPIs, rabeprazole has in vitro bactericidal activity against this organism, greater than either lansoprazole or omeprazole.

**FIGURE 4.** pKa and clinical efficacy of PPIs

Source: Reference 31.

The drug, in addition to inhibiting bacterial urease activity, binds to several molecules on *H. pylori*.<sup>34</sup> The outlook may be particularly relevant in countries like India, where *H. pylori* chronically infects more than 70% of the population.<sup>35</sup>

## Safety of potent gastric acid inhibition

The PPIs are very effective drugs for the control of gastric acid secretion, and are of great utility in the medical practice setting. In fact, they are prescribed in all age populations, quite often in polymedicated patients with pluripathology, and on many occasions PPIs are prescribed for prolonged periods. The risk of drug interactions, when prescribed together with other drugs, is low and their repercussion in the medical practice setting is quite exceptional, seeing that they require few dosage adjustments in patients with severe concomitant diseases and in elderly patients.<sup>36</sup>

Notwithstanding benefits of PPIs, their long-term safety has been questioned recently.<sup>37</sup> Apprehensions regarding their tolerability – at least partly – stem from reports demonstrating modest increase in the risk of hip and vertebral fracture associated with their use. However, these results are equivocal and have not been consistently shown in all studies. Some investigators also have suggested risk of *Clostridium difficile* (*C. difficile*) infection subsequent to PPI use.<sup>38</sup> However, despite these reports, almost all PPIs have been shown to be safe in long-term treatment.

## A CLOSER LOOK AT OTHER EMERGING THERAPIES

Novel approaches to blocking acid secretion, such as gastrin (CCK2) receptor antagonists and potassium-competitive acid blockers (P-CABs), are being explored in clinical development, widely driven by the surge for new methods of controlling acid secretion.<sup>20</sup> It is probable that gastrin receptor antagonists would be used adjunctively with PPIs, possibly for meal-induced reflux. In contrast, the potassium-competitive acid blockers have attributes that may facilitate their use as monotherapy for the treatment of GERD. Other as yet unrealized strategies of potential approach for acid inhibition include histamine receptor subtype 3 agonists, prevention of the fusion of

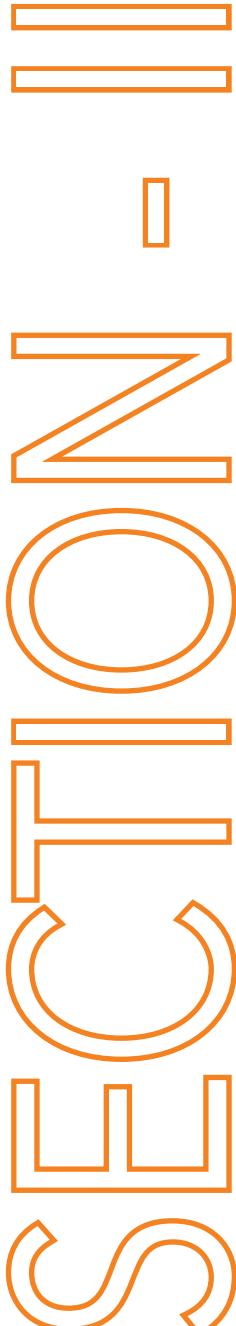
the tubulovesicular elements that contain H<sup>+</sup>/K<sup>+</sup>-ATPase with the parietal cell membrane, or blockage of channels that recycle K<sup>+</sup> in the parietal cell.

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Widely facilitating the empiric approach for acid peptic disorders, as mentioned in this section, we cover GERD and PUD, the most common acid peptic disorders, and other acid related disorders with similar presentations in the following sections.

# GASTROESOPHAGEAL REFLUX DISEASE



## GERD – THE REFLUX MANIFESTATION OF ACID PEPTIC DISEASES

Gastroesophageal reflux disease (GERD), a widely prevalent acid-related disorder, has emerged as one of the most common diseases in modern civilization, with significant impairment and serious consequences for the health-related quality of life.<sup>1-3</sup> The disease occurs when stomach acid frequently backs up (or refluxes) into the gullet (or esophagus), this being usually felt as heartburn. Importantly, gastroesophageal reflux is the most common cause of heartburn.<sup>4</sup>

### GERD versus NERD

While reflux leads to altered clearance and impaired protective mechanisms in the esophagus, and the disease continuum includes patients with esophageal mucosal injury, usually erosive esophagitis, it is estimated that about 50–70% of GERD patients are without esophagitis; such patients are referred to as having non-erosive gastroesophageal reflux disease (NERD).<sup>5</sup>

#### *The paradox of NERD*

NERD accounts for the majority of GERD diagnoses, being referred to as functional heartburn, and defined as “retrosternal burning in the absence of pathological gastroesophageal reflux, pathology-based motility disorders or structural explanations.”<sup>6,7</sup> Of note, the condition is difficult to assess, while negative endoscopic findings in such a setting do not generally correlate with symptom severity. This implies that a NERD patient may have a negative endoscopy and severe symptoms of heartburn, theoretically explained by esophageal hypersensitivity that is believed to result from lowered mucosal immunity and inflammation, allowing refluxate effective access to intercellular spaces, causing dilation of the intercellular spaces and resulting in constituent symptoms of esophageal pain or heartburn. In addition, psychological stress has also been shown to account for increased perception of esophageal pain in NERD. Box 1 shows characteristic differentiating features for NERD.<sup>6</sup>

#### BOX 1. Differentiating features of NERD

- NERD patients are less likely to have abnormal esophageal exposure to gastric contents and lower nighttime esophageal acid exposure than those with erosive esophagitis.
- NERD patients have decreased peristalsis that is less severe than those with erosive esophagitis.
- NERD patients have only mildly reduced lower esophageal sphincter pressure.
- Hiatal hernia, a major risk factor for reflux esophagitis, occurs in only 29% of NERD diagnoses compared to 71% of those with erosive esophagitis.

Source: Reference 6.

## Epidemiology of GERD – Asians particularly at risk

Being a global problem, GERD is more and more commonly found in daily medical practice worldwide; however, its prevalence appears to be rising particularly in Asia.<sup>8,9</sup> Despite this, there exists a paucity of studies reporting the prevalence of GERD in eastern and southeastern Asia. The reported population prevalence of GERD in eastern Asia was found to range from 2.5% to 6.7% for at least weekly symptoms of heartburn and/or acid regurgitation, and may be increasing<sup>10</sup>; whereas, in case studies, the prevalence of reflux esophagitis ranged from 3.4% to 16.3%. Table 1 shows certain well-established risk factors for GERD in Asian populations.<sup>10</sup>

**TABLE 1.** Risk factors for GERD in Asian populations

Well-established risk factors	Hiatus hernia Obesity
Other possible risk factors	Age Male sex

Source: Reference 10.

## A CLOSER LOOK AT THE PATHOGENESIS AND PATHOPHYSIOLOGIC MECHANISMS

Development of GERD and its constituent symptoms may be attributable to a multifactorial etiology, the disease being thought to develop when a combination of conditions occurs that increase the presence of refluxed acid in the esophagus to pathologic levels, and when aggressive mechanisms, potentially harmful to the esophagus, overwhelm protective mechanisms, similar to that of other acid-secretory disorders.<sup>11</sup>

Figure 1 depicts multiple mechanisms that are thought to contribute to the development of this pathologic setting of GERD.<sup>11,12</sup> While a significant defect in any one of these forces can lead to symptoms and complications such as heartburn and esophagitis, the most common causative mechanism in GERD is due to transient lower esophageal sphincter (LES) relaxations (TLESRs). Additionally, a pathologically decreased LES resting tone is more common among patients with severe GERD, especially those with esophageal strictures or Barrett's esophagus. Finally, once reflux has occurred, impaired acid clearance prolongs exposure of the mucosa to the damaging effects of the refluxate. Furthermore, though diminished peristaltic clearance is seen among roughly one half of patients with severe GERD, this acid clearance is particularly impaired in patients with hiatal hernia, which is present in ≥ 90% of patients with severe erosive esophagitis.<sup>12</sup>

**FIGURE 1.** Possible etiopathologic factors involved in GERD



Source: References 11,12.

## DIAGNOSIS OF GERD

Frequently, a diagnosis of GERD can be made based on a history of classic symptoms, without requiring additional diagnostic testing, and favorable response to antisecretory medical therapy.<sup>13</sup> This becomes all the more relevant given that there exists no standard criterion, and no gold standard test, for the diagnosis of GERD, and diagnostic studies have several limitations. During esophagogastroduodenoscopic evaluation of GERD patients, about one-third are found to have erosive esophagitis, with lesions characteristically representing esophageal mucosa exposure to gastric refluxate.<sup>14</sup> The Los Angeles (LA) classification system is used when describing the endoscopic appearance of erosive esophagitis (Table 2).<sup>15-17</sup>

**TABLE 2.** The Los Angeles (LA) classification system for the endoscopic appearance of reflux esophagitis

Severity grade	Endoscopic appearance
A	≥ 1 mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
B	≥ 1 mucosal breaks > 5 mm, none of which extends between the tops of the mucosal folds
C	Mucosal breaks extending between the tops of ≥ 2 mucosal folds, but not circumferential (<75% of circumference)
D	Mucosal breaks involving at least 75% of the esophageal circumference (circumferential)

Source: References 15-17.

Diagnostic difficulties are greatest when reflux symptoms occur without visible esophageal mucosal damage at conventional endoscopy, though two thirds of such patients do have microscopic esophageal lesions.<sup>18</sup> Regardless, a short course of proton pump inhibitor (PPI) therapy is often used in clinical practice as a “diagnostic” test for GERD.<sup>8</sup>

## Symptoms and clinical features

In practice, a delay in consultation at clinic may in part be attributable to the fact that patients often present when symptoms reach a threshold where they constitute “disease” and are troublesome to them.<sup>13</sup> Classical symptoms of heartburn and regurgitation are common presentations of GERD.<sup>8,19</sup> However, besides these cardinal symptoms, GERD patients can also present with sleep disturbances, chest pains, or respiratory symptoms (Figure 2).<sup>4,8,19-22</sup> In essence, the manifestations of GERD can be divided into esophageal and extraesophageal syndromes, consistent with Montreal classification, with extraesophageal syndromes being divided into established and proposed associations (Figure 3).<sup>4,22</sup>

**FIGURE 2.** Clinical presentations in GERD

Typical Symptoms	Heartburn, acid regurgitation
Atypical Symptoms	Belching, epigastric pain
Complications	ENT (e.g., chronic cough, hoarseness, laryngitis, pharyngitis, sinusitis, otitis, globus)
	PULMONARY (e.g., asthma, chronic bronchitis, idiopathic fibrosis, pneumonia)
	MISCELLANEOUS (e.g., dental erosion, halitosis, non-cardiac chest pain, sinus arrhythmia, sleep apnea)
	Esophageal erosion and/or ulcer
	Strictures
	Barrett's esophagus
	Esophageal adenocarcinoma

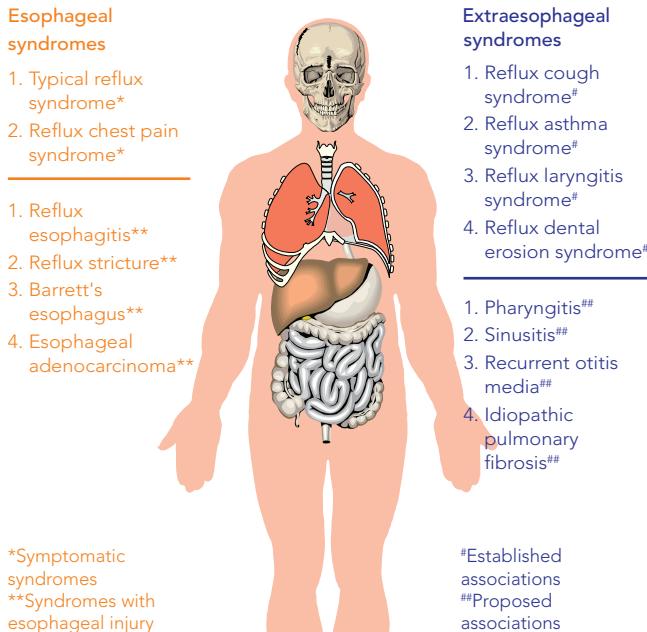
Source: References 4,8,19-22.

## Extraintestinal manifestations of GERD – the rising concern

GERD often manifests clinically when the gastroesophageal reflux is accompanied by inflammation of the esophageal mucosa, but many patients report symptoms outside the esophagus<sup>23</sup>; chest pain is a predominant extraesophageal manifestation of GERD (Figure 4 & 5)<sup>24,25</sup>, and a link with asthma has also been implicated in patients with severe

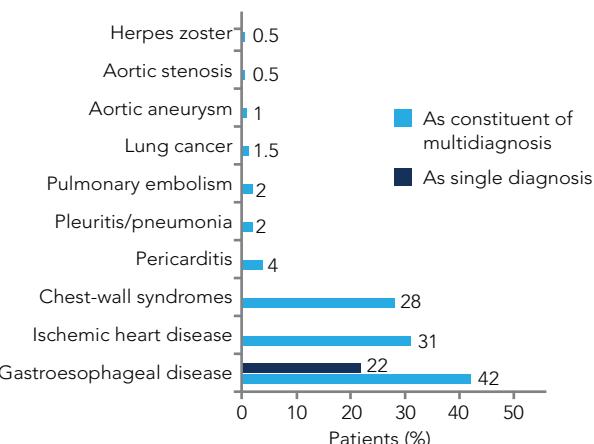
**FIGURE 3.** GERD and its constituent syndromes as per Montreal classification

GERD is a condition which develops when the reflux of gastric content causes troublesome symptoms or complications



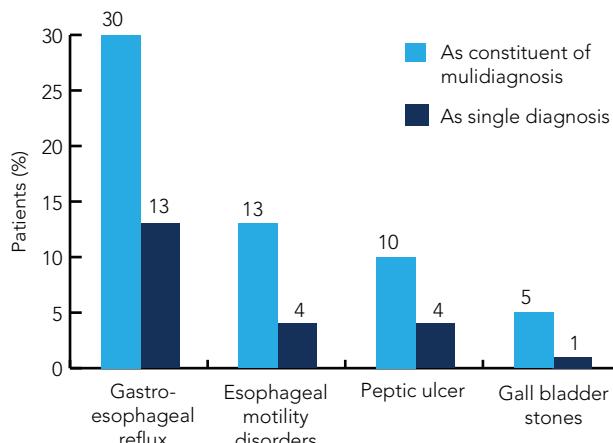
Source: References 4,22.

**FIGURE 4.** Frequency of diagnoses in patients admitted with acute chest pain who have not had myocardial infarctions



Source: References 24,25.

**FIGURE 5.** Distribution of the different diagnosis in non-acute myocardial infarction patients with gastroesophageal disorders

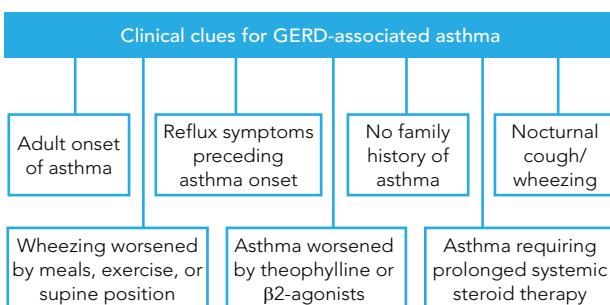


Source: Reference 24.

esophagitis.<sup>10</sup> Thus, the clinical picture may include lesions of the esophageal mucosa together with lesions of the respiratory and stomatognathic apparatus<sup>23</sup> including asthma and chronic cough, otolaryngologic findings and symptoms, and other extraesophageal manifestations, including dental erosions. GERD is also frequently associated with sleep disturbance.<sup>4</sup>

Though the exact nature of the relationship between GERD and asthma is unclear, putative mechanisms include microaspiration of acid into the larynx and pharynx, vagally mediated bronchospasm, and laryngospasm.<sup>26,27</sup> Nevertheless, the role of extraesophageal reflux in such disorders is under-diagnosed possibly because of the often-silent symptoms and difficult confirmation of diagnosis.<sup>27</sup> This makes it particularly important that the clinicians be aware

**FIGURE 6.** Clinical clues useful in the diagnosis of GERD-associated asthma



Source: Reference 20.

of the possibility of these reflux-related extraesophageal conditions, even in the absence of classic esophageal symptoms of GERD. Laryngeal examination and quantitative evaluation of findings using the reflux finding score are very useful in making the diagnosis and planning treatment, and a number of clinical clues can themselves be helpful in identifying GERD-related asthma (Figure 6).<sup>20</sup> Long-term high-dose PPI therapy is generally the first-line approach to controlling symptoms<sup>20</sup>, though the treatment response is less predictable than it is for typical GERD.

### Oral manifestations of GERD

GERD is increasingly considered a multifaceted disorder resulting in a wide spectrum of clinical and morphological manifestations secondary to the reflux.<sup>23</sup> Several research publications have documented an association between GERD and dental erosions, although some opinions differ on whether GERD is truly the cause of dental disease.<sup>28</sup> Nonetheless, as adequate salivary secretion is essential for the protection of the teeth and the oropharyngeal and esophageal mucosa, strategies might be needed to promote adequate saliva production in patients with significant GERD, in addition to controlling acid secretion.<sup>28</sup>

### The complex relationship between GERD and eosinophilic esophagitis

The suggested interaction between GERD and eosinophilic esophagitis makes establishing a clear distinction between the two disorders somewhat difficult, especially in situations wherein GERD may be associated with esophageal eosinophilia (Box 2). In fact, the high frequency of GERD described in adult patients with eosinophilic esophagitis suggests more than a chance association between the two disorders, and GERD might contribute to the accumulation of eosinophils in the esophageal epithelium through a number of plausible mechanisms.<sup>29</sup> Furthermore, it is suggested that a favorable response to PPI therapy does not preclude a diagnosis of eosinophilic esophagitis, though it is recommended that patients undergo a trial of PPI therapy before the diagnosis of eosinophilic esophagitis is made.<sup>30</sup>

### BOX 2. Situations where GERD may be associated with esophageal eosinophilia

- GERD causes esophageal injury that results in a mild eosinophilic infiltration
- GERD and eosinophilic esophagitis coexist but are unrelated
- Eosinophilic esophagitis contributes to or causes GERD, or
- GERD contributes to or causes eosinophilic esophagitis.

Source: Reference 29.

## Frequently-used diagnostic modalities

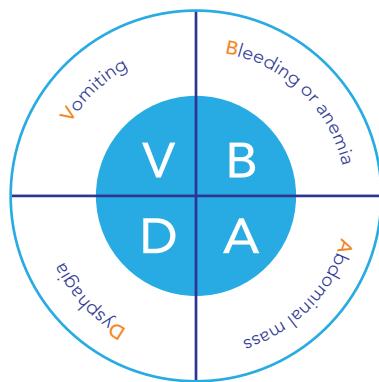
### 24-hour ambulatory monitoring

Continuous esophageal pH monitoring with catheter-based pH probes and wireless pH probes (with or without impedance monitoring) is useful in confirming abnormal acid exposure in cases where the clinical picture is confusing, or when there is a failure of response to PPI therapy. A 24-hour pH study has sensitivity and specificity values of more than 90% for the diagnosis of GERD. The technique measures the duration and frequency of episodes in which the pH falls below 4, and computer software is used to collect and analyze the data. As follows, this 24-hour esophageal pH monitoring is an important way to predict abnormal acid exposure.<sup>31</sup> Even so, though GERD can be diagnosed objectively with endoscopy or 24-hour pH/impedance monitoring with symptom association analysis, 24-hour pH monitoring lacks sensitivity in NERD.<sup>32</sup>

### Endoscopy

Endoscopy is one of the most frequently used diagnostic modalities in gastroenterology. However, care should always be taken to identify patients who might benefit from upper gastrointestinal endoscopy because they have alarm features or are advanced in age (as the risk of upper gastrointestinal malignancy increases each year after age 50). Thus, all patients over 50 years of age who present with new-onset dyspepsia and patients who present with alarm features should receive prompt endoscopy. The acronym "VBAD" may prove beneficial in remembering these alarm features (Figure 7), which include (persistent) vomiting, evidence of

**FIGURE 7.** Alarm features prompting further investigation by endoscopy



Source: References 25,33.

gastrointestinal bleeding or anemia, abdominal mass or unexplained weight loss, and dysphagia.<sup>25,33</sup>

## TREATMENT OF GERD

In GERD, both symptom severity and esophageal injury correlate with the degree of acid exposure, thereby demonstrating a positive relationship between intragastric acid control and erosive esophagitis healing. Here, pathological reflux is determined by the percentage of time with esophageal pH <4.0, or, conversely, acid control can be defined by the time during which the pH level remains >4.0.<sup>14,19</sup> As follows, the goals of GERD treatment are to control symptoms, maintain a stable non-inflamed esophageal mucosa, and prevent complications.<sup>34</sup> In such setting, uninvestigated heartburn-dominant dyspepsia – characterized by heartburn or acid regurgitation – may be treated empirically as GERD without further investigation, provided there are no alarm features.<sup>3,35</sup>

### The choice of medical therapy

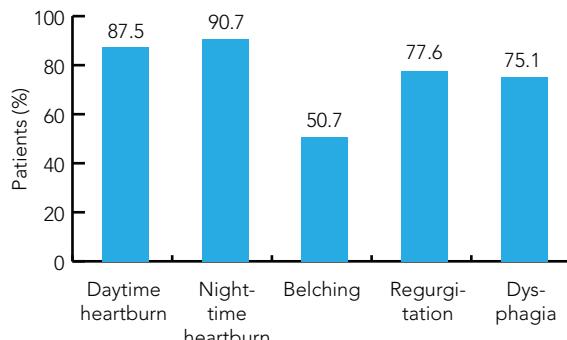
The choice of a medical therapy to treat GERD is based on several factors, including the efficacy and safety of the agent and the severity of the patient's symptoms and complications. In this regard, acid-suppressive agents have become the drugs of choice for GERD. While both PPIs and histamine H<sub>2</sub>-receptor antagonists effectively and safely treat GERD, PPIs have been shown to provide the highest levels of GERD symptom relief and esophageal healing to the most patients in the shortest time.<sup>36</sup> Table 3 shows the dosage of available PPIs used for healing for erosive esophagitis.<sup>16</sup> Essentially, they provide an excellent outcome for the majority of GERD patients, and thus remain the mainstay of treatment for GERD.<sup>8</sup> Indeed, they promote faster symptom relief in not only reflux disease but also non-erosive reflux disease.<sup>19</sup>

**TABLE 3.** Once daily doses of available PPIs for erosive esophagitis

Proton pump inhibitor	Daily dose
Esomeprazole	40mg
Pantoprazole	40mg
Lansoprazole	30mg
Omeprazole	20mg
Rabeprazole	20mg

Source: Reference 16.

**FIGURE 8.** Patients with endoscopy-confirmed erosive esophagitis showing complete relief of symptoms with once-daily rabeprazole (20 mg) by week 4



Source: Reference 37.

Pertinent clinical evidence by Cutler et al<sup>37</sup> showed that in patients with endoscopy-confirmed erosive esophagitis treated with once-daily rabeprazole (20 mg), treatment resulted in prompt and sustained improvement in daytime and nighttime heartburn, belching, regurgitation, and dysphagia. By week 4, complete relief of daytime and nighttime heartburn, belching, regurgitation, and dysphagia was observed in 87.5, 90.7, 50.7, 77.6, and 75.1% of patients, respectively (Figure 8).<sup>37</sup> In addition, another comparative study showed that, in GERD patients with nocturnal heartburn, rabeprazole 20 mg was significantly more effective than pantoprazole 40 mg in percentage time with intragastric pH >4 during the nighttime, daytime, and 24-hour periods.<sup>38</sup>

Of note, such an empirical acid-suppressive therapy with a PPI can assist clinicians in identifying patients with undiagnosed chest pain whose symptoms are acid-related<sup>39</sup>; Kim et al<sup>40</sup> observed that an empirical trial of rabeprazole was diagnostic for patients with GERD-related non-cardiac chest pain, and its optimal duration was determined to be at least two weeks.

Monitoring patients' response to PPI therapy can confirm the success of management. Response to initial therapy, i.e., a once-daily PPI, should be assessed at four to eight weeks given that an 8-week treatment with PPIs is satisfactory in most cases (> 90%) with typical GERD symptoms.<sup>41</sup>

Maintenance medical therapy should be at the lowest dose and frequency necessary to maintain symptom relief.<sup>3</sup> This is consistent with the concept that pharmacological therapy is effective not only in producing acute symptom relief and mucosal healing, but also in the long-term maintenance of remission.<sup>42</sup> In fact, Fujimoto et al<sup>43</sup> confirmed rabeprazole 10 mg to be safe and effective for maintenance therapy in patients with reflux esophagitis – the endoscopic

non-relapse rate for reflux esophagitis was 87.3% for the two-year (104-week) period.

Routine testing for *H. pylori* infection is not necessary before starting GERD therapy.<sup>3</sup> However, in addition to drug therapy, life-style modification should be recommended as follows: sleep with a 30–45 degree elevation of the head or upper chest, avoid fatty or fried foods, reduce stress, stop smoking, eat small but frequent meals, etc.<sup>44</sup> Weight loss is recommended for those who are overweight or have had recent weight gain.<sup>15</sup>

## Surgery and endoscopic therapies

Large randomized clinical trials and more than 16 years of worldwide experience have confirmed the high rate of efficacy and excellent safety profile of PPI therapy in individuals with all grades of GERD, making these agents the mainstay of treatment.<sup>34</sup> However, despite the favorable outcomes with pharmacotherapy, some individuals may desire an alternative intervention. In a small proportion of selected patients, antireflux surgery, laparoscopic fundoplication, is an alternative that may produce symptom relief and the healing of esophagitis<sup>3,8,45</sup>; however, its invasiveness, cost, and inherent surgical risks have created an interest in a variety of endoscopic therapies for reflux disease. These endoscopic therapies have been reported to have encouraging preliminary results in several short-term uncontrolled trials; however, careful patient selection in addition to clinician expertise is critical for their success. Success with endoscopic GERD therapy has been observed only in patients with non-erosive GERD and a hiatal hernia <3 cm, with abnormal pH monitoring and normal esophageal motility studies, as well as in those who have experienced at least partial symptom relief with PPI therapy. Endoscopic therapy should not be considered the standard of care in patients with erosive disease or large hiatal hernias.<sup>34</sup>

These endoscopic interventions may either be viewed as an alternative therapy or as 'bridge' therapy, as patients generally choose to be treated with acid anti-secretory drugs or fundoplication if the endoscopic procedure fails to provide adequate symptom relief, or if symptoms recur. Patient selection is critical for the success of both fundoplication and endoscopic procedures.<sup>46</sup> In this regard, ideal candidates are those with well-established endoscopically documented GERD, abnormal pH monitoring, normal esophageal motility studies, and who have experienced at least partial symptom relief with PPI therapy. Whilst hiatal hernia is not a contraindication to fundoplication, in contrast, as also mentioned earlier, endoscopic intervention is best suited for those with a hiatal hernia of <3 cm in length.<sup>42</sup>

While the effectiveness of surgical fundoplication in treating classical reflux symptoms is well documented, the role of surgery in alleviating extraesophageal reflux

symptoms is less clear. The majority of patients seem to improve symptomatically after surgery; however, a small percentage remains unchanged or worsens.<sup>47</sup> Recently, robot-assisted laparoscopic fundoplication (RALF) was considered a new approach to make up for the deficiency of conventional laparoscopic fundoplication.<sup>48</sup> However, this modality, despite being a feasible and safe alternative to surgical treatment of GERD, has disadvantages with respect to operating time, length of hospital stay and cost.

### Radiofrequency ablation of LES

Studies of endoscopic application of radiofrequency energy to the lower esophageal sphincter for control of gastroesophageal reflux have produced conflicting reports of effectiveness. Yet, such radiofrequency ablation of the LES produces significant improvement in reflux symptoms in selected patients, and may represent an alternative to medical treatment and surgical fundoplication.<sup>49</sup>

## COMPLICATIONS OF GERD

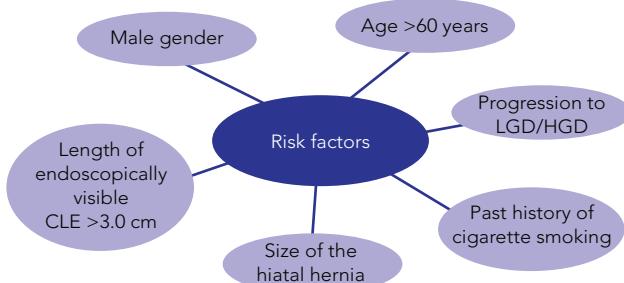
The continuum of GERD complications ranges from erosive esophagitis to esophageal cancer, all occurring due to repeated exposure of the esophagus to caustic gastric acid. Although progression from one complication to another is not clearly established across this continuum, there is a clear progression from the significant complication of Barrett's esophagus to esophageal adenocarcinoma.<sup>21</sup>

Therefore, heartburn should be considered as a symptom of a potentially serious condition in the setting of chronic GERD. In effect, endoscopic screening for Barrett's epithelium may be considered in adults with GERD symptoms for > 10 years given that the presence of Barrett's epithelium warrants endoscopic surveillance, together with the consideration of endoscopic or surgical management if there is confirmed high-grade dysplasia or malignancy.<sup>3</sup>

### The progression of Barrett's esophagus to esophageal adenocarcinoma

Only a minority of patients with chronic GERD actually develop Barrett's esophagus, suggesting that there must exist other risk factors that modulate reflux-related inflammatory and pro-neoplastic effects on esophageal epithelium.<sup>50</sup> Esophageal adenocarcinoma develops along a sequence from non-dysplastic Barrett's esophagus (NDBE), to low- (LGD) and then high-grade dysplasia (HGD).<sup>51</sup> A review conducted to examine the annual cancer risk for persons with NDBE and symptoms of GERD documented a low published annual cancer risk for symptomatic NDBE, ranging from 0.12-0.5% and 0.33-0.7% in population-based studies and meta-analyses, respectively. A number

**FIGURE 9.** Risk factors for esophageal cancer development



CLE - columnar lined esophagus ; LGD - low grade dysplasia; HGD - high grade dysplasia.

Source: Reference 51.

of risk factors were identified for cancer development (Figure 9).

The mean time-to-cancer development was 5 years, and ranged from two to 15 years; age at the diagnosis of symptomatic NDBE and cancer development was found to plateau at around 50 and 60 years of age, respectively. The epidemiologic data have prompted the initiation of chemopreventive trials using aspirin and PPIs in the treatment of Barrett's esophagus and esophageal adenocarcinoma.

### Role of potent gastric acid inhibition in the management of Barrett's esophagus

The therapeutic objectives in Barrett's esophagus, the consequence of excessive and prolonged gastroesophageal reflux, include the reduction of gastroesophageal reflux in order to relieve symptoms, and the prevention of the biologic progression to adenocarcinoma. The first objective may be achieved with standard PPI therapy, which is the basis of the medical therapy in such patients; however, it has been found that standard therapy may not be associated with normalization of the intraluminal pH of the esophagus in patients with Barrett's esophagus.<sup>52</sup> Thus, it has been proposed that patients with Barrett's esophagus require profound acid inhibition with high-dose PPI therapy. Again, though this therapeutic approach provides symptom relief, there is no direct evidence that it is associated with Barrett's esophagus regression or decreased progression to adenocarcinoma, though preliminary data suggest that long-term PPI therapy may reduce the risk of disease progression. This profound acid inhibition may be provided in conjunction with endoscopic ablative therapy in patients with Barrett's esophagus. Nonetheless, more data are needed before therapeutic role of this experimental approach is established in patients with Barrett's esophagus.

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## Guidelines for the Diagnosis and Management of GERD

### DIAGNOSIS

- Empiric medical therapy with a proton pump inhibitor (PPI) is recommended in the setting of typical symptoms of heartburn and regurgitation to establish a presumptive diagnosis of GERD.
- In patients with chest pain, a cardiac cause should be excluded before the commencement of a gastrointestinal evaluation.
- Barium radiographs should not be performed for the diagnosis of GERD.
- The presence of typical GERD symptoms makes upper endoscopy unnecessary. However, endoscopy is recommended in presence of alarm symptoms and for screening of patients at high risk for complications.
- Though recommended for preoperative evaluation, esophageal manometry has no role in the diagnosis of GERD.
- Screening for *H. pylori* infection is not recommended in patients with GERD.

### MANAGEMENT

- Weight loss is recommended for GERD patients who are overweight.
- An eight-week course of PPIs is the therapy of choice for symptom relief and healing of erosive esophagitis, initiated at once a day dosing, before the first meal of the day.
- Tailored therapeutic regimens, with adjustment of dose timing and/or twice daily dosing should be considered in patients with nighttime symptoms, variable schedules, and/or sleep disturbance if there is partial response to once daily therapy.
- It is recommended that maintenance PPI therapy be administered if GERD patients continue to have symptoms after PPI is discontinued, and in those with complications like erosive esophagitis and Barrett's esophagus.
- Therapy for GERD other than acid suppression, such as prokinetic therapy, should not be considered without diagnostic evaluation.
- Treatment of *H. pylori* infection is not routinely required as part of anti-reflux therapy.

### SURGICAL THERAPY

- Surgery is a treatment option for long-term therapy in patients with GERD. Yet, it is generally not recommended in patients who do not respond to PPI therapy.
- It is mandatory that preoperative ambulatory pH monitoring be performed in patients without evidence of erosive esophagitis. Besides, all patients being considered for surgery for GERD should undergo preoperative manometry to rule out achalasia or scleroderma-like esophagus.
- When performed by an experienced surgeon, surgical therapy has comparable effectiveness to medical therapy for carefully selected patients with chronic GERD.

**Source:** Katz PO, Gerson LB, Vela MF, et al. Am J Gastroenterol 2013;108:308-328.

# PEPTIC ULCER DISEASE



## The journey of peptic ulcer disease

Initially, the secretion of acid was thought to be the overwhelming cause of peptic ulcer disease (PUD), supporting the dictum ‘no acid, no ulcer’. This finding led to the use of therapy directed against intragastric acidity, which also interfered with pepsin activity when the pH was  $> 4$ . Therapeutic options progressed from large doses of antacids to H<sub>2</sub>-receptor antagonists and finally to proton pump inhibitors (PPIs). It was demonstrated that the longer the intragastric pH was  $> 3$ , the more rapidly the ulcers healed. Unfortunately, ulcers often recurred after discontinuation of therapy, thus raising the demand for maintenance therapy to prevent ulcer recurrence and to reduce the need for surgical intervention (vagotomy, partial gastric resection). Over time, the emphasis gradually shifted to the weakening or failing of the defensive factors in the stomach that raised the vulnerability of the gastroduodenal mucosa to luminal secretions.<sup>(i)</sup>

Numerous injurious mechanisms jeopardizing the mucosal integrity were subsequently identified: infections, especially *Helicobacter pylori* (*H. pylori*); drug-induced injury, particularly acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs); physicochemical and caustic injury; vascular disorders, interfering with perfusion, etc. Of these multiple mechanisms, *H. pylori* infection was identified as the leading cause of PUD. Nonetheless, the incidence of *H. pylori* and NSAID negative PUD has increased over the last two decades, especially in the Western world and in countries with low *H. pylori* infection rates. As follows, idiopathic PUD is a recently described entity that relates to peptic ulcers not caused by *H. pylori*, NSAID/aspirin therapy, other known ulcerogenic organisms and drugs, or other rare malignant and benign diseases.<sup>(ii)</sup>

Source:

(i) Tytgat GN. *Dig Dis.* 2011;29(5):454-8.

(ii) Niv Y, Boltin D. *Digestion.* 2012;86(3):258-63.

## PUD – THE ULCEROUS MANIFESTATION OF ACID PEPTIC DISORDERS

Worldwide, peptic ulcers and their complications remain a cause of significant morbidity, particularly in older age groups, and represent a major burden for ambulatory and hospital healthcare resources.<sup>1</sup> Peptic ulcer disease (PUD) is the cause of dyspepsia in about 10% of patients<sup>2</sup>, and usually occurs in the stomach and proximal duodenum; it is due mostly to the widespread use of low-dose aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) in synergism with *Helicobacter pylori* (*H. pylori*) infection.<sup>3</sup>

## ETIOPATHOGENETIC PRINCIPLES AND PUD CLASSIFICATION – THE ATTACK AND THE DEFENSE

Ulcers correspond to mucosal tissue loss, breaching the muscularis mucosae, and when they develop in the acid peptic environment of the gastroduodenum, the condition is traditionally referred to as PUD. Ulcers, though never developing spontaneously in a healthy gastroduodenal mucosa, are the ultimate consequence of disequilibrium between aggressive injurious factors and defensive mucosa-protective factors (Figure 1).<sup>4</sup>

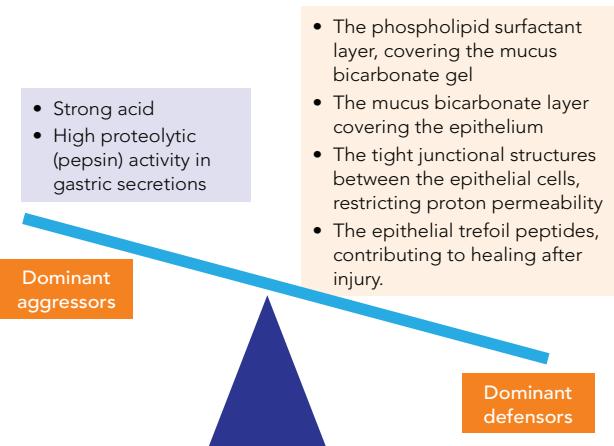
## EPIDEMIOLOGY OF PUD

The epidemiology of PUD has undergone significant changes since the discovery of *H. pylori*.<sup>5</sup> Until the last decades of the 20<sup>th</sup> century – when epidemiological studies began to report an impressive decrease in incidence – PUD had a tremendous effect on morbidity and mortality worldwide. This decrease in incidence rates might be attributable to two important developments: the discovery of effective and potent acid suppressants, and the recognition of *H. pylori* as a cause of PUD.<sup>6</sup> Nonetheless, with the continued presence of *H. pylori* infection throughout the world and the widespread use of acetylsalicylic acid and NSAIDs, PUD remains a relatively common condition, although reported incidence and prevalence of gastric and duodenal ulcers are decreasing, which may be attributable to a decrease in *H. pylori*-associated PUD in the general population of developed countries.<sup>7</sup>

### Global incidence and prevalence

The management of *H. pylori* infection has improved significantly in recent years; in contrast, the prescription of acetylsalicylic acid and NSAIDs has increased over the same period. A systematic literature review by Sung et al<sup>8</sup>,

**FIGURE 1.** Aggressive injurious factors and defensive mucosa-protective factors in gastroduodenum



Source: Reference 4.

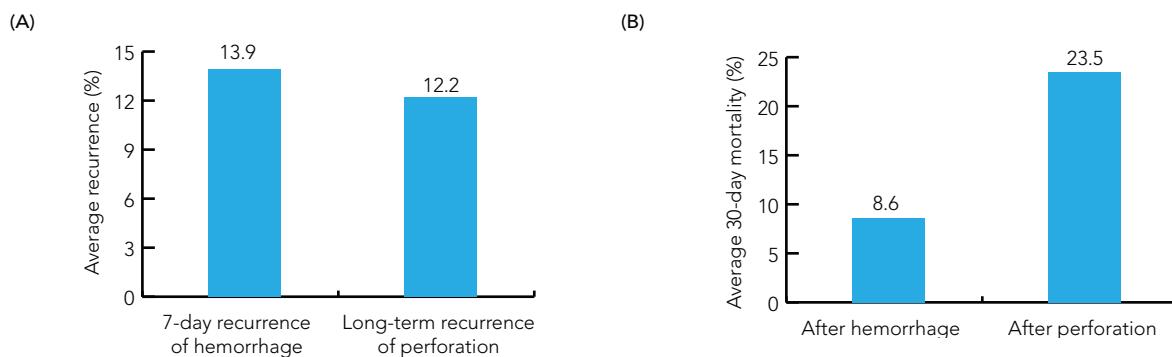
to evaluate the global incidence and prevalence of PUD, found the annual incidence rates of PUD to be 0.10-0.19% for physician-diagnosed PUD and 0.03-0.17% when based on hospitalization data. Similarly, the 1-year prevalence based on physician diagnosis was 0.12-1.50% and that based on hospitalization data was 0.10-0.19%.<sup>8</sup>

Nevertheless, it has been observed that the estimated incidence rates for PUD vary widely among studies. Lin et al<sup>9</sup> conducted a systematic review to quantify and examine these discrepancies. The authors found that the incidence rate of uncomplicated PUD was in the order of one case per 1000 person-years in the general population, and that the incidence rate of peptic ulcer complications was around 0.7 cases per 1000 person-years. Younger age and female sex were associated with lower PUD incidence.<sup>9</sup>

### Epidemiology of complicated PUD

Though the incidence of uncomplicated peptic ulcer has decreased in recent years, complicated peptic ulcer remains a substantial healthcare problem as it places patients at a high risk of recurrent complications and death. In a systematic review, Lau et al<sup>10</sup> aimed to determine the incidence, recurrence and mortality of complicated peptic ulcer and the risk factors associated with these events. The results identified that the annual incidence estimates of peptic ulcer hemorrhage and perforation were 19.4-57.0 and 3.8-14 per 100,000 individuals, respectively. The average 7-day recurrence of hemorrhage was 13.9%, and the average long-term recurrence of perforation was 12.2% (Figure 2A).<sup>10</sup>

**FIGURE 2.** (A) Average recurrence of hemorrhage and perforation seen with complicated peptic ulcer  
 (B) Average 30-day mortality after hemorrhage and perforation seen with complicated peptic ulcer



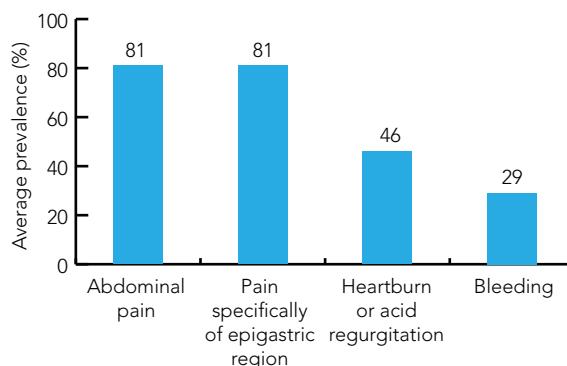
Source: Reference 10.

Risk factors for peptic ulcer complications and their recurrence included: NSAIDs and/or acetylsalicylic acid use, *H. pylori* infection, and ulcer size  $\geq 1$  cm. Average 30-day mortality was 8.6% after hemorrhage and 23.5% after perforation (Figure 2B). Older age, comorbidity, shock and delayed treatment were found to be associated with increased mortality.<sup>10</sup>

### Symptom burden and quality of life impairment associated with PUD

Though the management of PUD has improved over the past few decades, the widespread use of NSAIDs and acetylsalicylic acid still makes the burden of PUD a relevant issue; this significantly impairs well-being and health-related quality of life, and is associated with high costs.

**FIGURE 3.** Average prevalence of reported symptoms in patients with symptomatic PUD



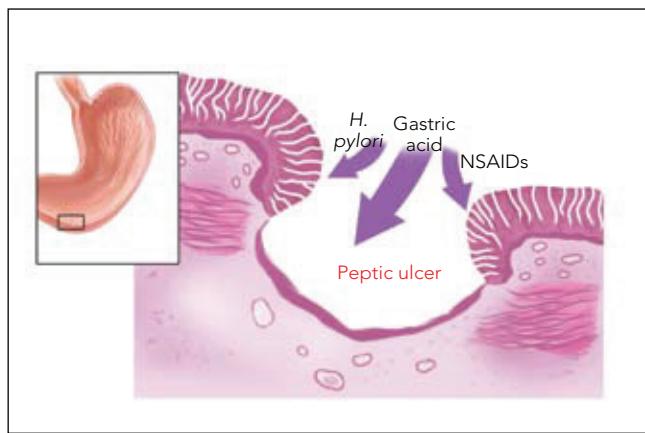
Source: Reference 11.

In a systematic literature review of articles that reported symptoms, impairment of well-being or health-related quality of life, and costs associated with PUD, Barkun *et al*<sup>11</sup> identified as many as 30 studies that reported the prevalence of patient-reported gastrointestinal symptoms in individuals with endoscopically diagnosed symptomatic PUD. Average prevalence of symptoms, weighted by sample size, was 81% for abdominal pain (11 studies), 81% for pain specifically of epigastric origin, and 46% for heartburn or acid regurgitation (11 studies) (Figure 3). On average, 29% of patients with PUD presented with bleeding, often as the initial symptom (11 studies). PUD patients had significantly lower health-related quality of life than the general population, as measured by the Psychological General Well-Being index ( $P < .05$ ; 7 studies) and the Short-Form-36 (SF-36) questionnaire ( $P < .05$ ; 2 studies). The most costly aspects of PUD management were hospitalization and medication, and this was particularly relevant for the cases of complicated PUD.

### CAUSES OF PUD

Various etiologies contribute to PUD, with gastric acid being but one factor in the pathogenesis of PUD. *H. pylori* infection and NSAID use represent independent and synergistic risk factors for uncomplicated and bleeding peptic ulcer (Figure 4).<sup>12-14</sup> In this regard, the etiologic agent may have an impact on ulcer localization as it has been seen that most duodenal ulcers are attributable to *H. pylori*, the biologic mechanism being increased acid output; by contrast, NSAID-induced ulcers occur more frequently in the stomach owing to alterations in mucosal defenses.<sup>15</sup>

While, in general, ulcers related to untreated *H. pylori* infection tend to recur, with antimicrobial therapy the

**FIGURE 4.** Pathogenesis of peptic ulcer disease

Source: References 12-14.

recurrence rate is extremely low. On the other hand, the use of NSAIDs, low-dose aspirin and dual anti-platelet therapy have become important risk factors for recurrent ulcers and their complications as the proportion of *H. pylori*-related ulcers declines. Furthermore, evidence suggests that *H. pylori*-negative, NSAID-negative idiopathic peptic ulcers are increasing in frequency and carry a higher risk of recurrent ulcer bleeding and mortality.<sup>16</sup> This rare but increasingly problematic *H. pylori*-negative NSAID-negative ulcer is clearly a growing concern.<sup>6</sup>

### Understanding the key role of *H. pylori* in PUD pathology

Many bacterial pathogens, such as *Escherichia coli*, *Salmonella Typhimurium*, and *H. pylori*, can circumvent the gastric acid conditions by developing adaptive mechanisms, allowing them to survive in the acidic stomach milieu, and many PUD cases originate from *H. pylori* infections<sup>17</sup>; in fact, about 95% of duodenal and 70% of gastric ulcers are thought to be associated with *H. pylori* infection. Worldwide, an estimated one billion people harbour the organism, and the highest prevalence is found in developing countries where up to 80% of people are infected, and where the most favored modes of transmission are fecal-oral and oral-oral.<sup>18</sup> This makes eradication of *H. pylori* in this setting an important goal in order to reduce the relapse rate of peptic ulcers; a 1 to 2 week course of *H. pylori* eradication therapy is an effective treatment for *H. pylori* positive peptic ulcer disease.<sup>2</sup>

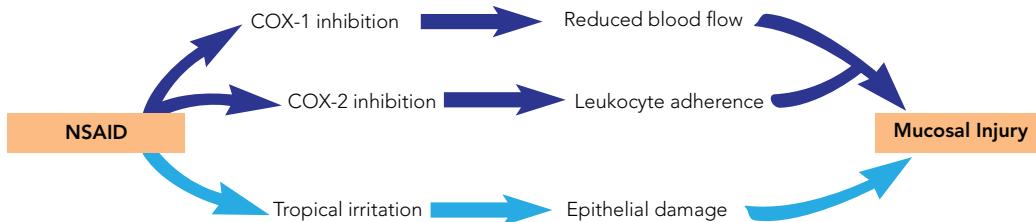
*The intriguing relationship of *H. pylori* infection and acid secretion in PUD – mechanisms of *H. pylori*-induced damage*

The mechanisms of *H. pylori*-induced gastroduodenal disease include various inter-related pathways, including the provocation of a local inflammatory reaction with the release of toxic cytokines, elevation of gastrin concentration, and cytotoxic epithelial injury from the activity of urease and other enzymes produced by the bacterium. However, the finding that a large proportion of infected persons have no disease or are asymptomatic suggests that there are other factors aside from *H. pylori* infection necessary for ulcer formation.<sup>18</sup>

*H. pylori* infection of gastric metaplasia causes an inhibition of HCO<sub>3</sub><sup>-</sup> secretion by its endogenous inhibitor dimethyl arginine, contributing to ulcerogenesis.<sup>19</sup> The chronic inflammation of the gastric mucosa due to the infection profoundly affects the gastric physiology, and gastric acid secretion is transiently impaired in the acute phase of infection. Essentially, all pertinent alterations attributable to this infectious process, i.e., the morphological damage of the gastric mucosa, changes in gastric hormone release, and disruption of neural pathways, all contribute to influence gastric acid secretion in a distinct manner. Ultimately, changes in gastric acid secretion, whether impaired or increased, have an effect on the phenotypes of gastritis and the presence of atrophy or absence of corpus atrophy. In effect, the interplay of gastritis phenotype and acid secretion are key determinants in disease outcomes. Whilst corpus-predominant gastritis and corpus atrophy are accompanied by hypochlorhydria and carry the highest risk for gastric cancer, the antrum-predominant gastritis with little involvement of the corpus-fundic mucosa is associated with hyperchlorhydria and predisposes to duodenal ulcer disease.<sup>20</sup>

### Role of the putative virulence markers (*cagA* and *vacA*) of *H. pylori* in PUD

The discovery of *H. pylori* has had a significant impact on the understanding of PUD pathophysiology. The organism is genetically diverse, with certain strains being more virulent and causing more severe disease than others, and such diversity is reflected in the clinical outcome. The cytotoxin-associated gene (*cagA*) and vacuolating cytotoxin (*vacA*) gene are two putative markers that were associated with PUD.<sup>21</sup> However, the exact basis for the epidemiological association between the *cagA* and *vacA* genes and PUD is not well known. Yet, it was observed that the *H. pylori* strains, *vacAs1bm1/cagA*-positive, were associated with increased risk of PUD, more robust lymphocytic and neutrophilic infiltrates in the stomach, and an increased incidence of intestinal metaplasia.<sup>22</sup>

**FIGURE 5.** Pathogenesis of NSAID-induced gastric damage

Source: Reference 24.

## NSAIDs induced damage

About 15–30% of regular NSAID users have one or more ulcers when examined endoscopically, and 3–4.5% have clinically significant upper gastrointestinal events, including ulcers and ulcer complications.<sup>23</sup> The mechanism for this NSAIDs induced damage includes suppression of both cyclooxygenase-1 (COX-1) and COX-2. While suppression of COX-1 might account for diminished gastric blood flow, suppression of COX-2 accounts for NSAID-induced leukocyte adherence to the vascular endothelium (Figure 5).<sup>24</sup>

## The likely role of mucin

Structural and secreted mucins create the unstirred gastric mucus layer and maintain a stable pH above the gastric mucosa. This mucus layer helps in preventing enzymatic attack of the mucosa by acid and pepsin. Inhibition of cyclooxygenase by NSAIDs and aspirin inhibits prostaglandin production, inhibits mucin and bicarbonate secretion, and exposes the mucosa to the toxic effects of acid and intragastric enzymes. Likewise, there also exists a complex relationship between *H. pylori* and different mucin subtypes, which on one hand facilitates bacterial invasion but on the other hand protects the gastric mucosa. As follows, genetic and epigenetic changes in this mucin molecule may also be responsible for idiopathic PUD, a hypothesis that should be further investigated.<sup>25</sup>

## Psychosocial factors in PUD: beyond *H. pylori* and NSAIDs

Of the multiple organic etiologies associated with PUD, the most relevant are infection with *H. pylori* and use of NSAIDs. Yet, between 5% and 20% of patients with gastric or duodenal ulcer lack an identifiable organic etiology. Particularly in these patients, and in ulcer patients in general, psychosocial factors may play a contributing role.<sup>26</sup> However, there is insufficient evidence for a clear causal relationship

between psychological stress and the development of ulcer disease. Nonetheless, a conservative application of available data would suggest that psychosocial factors do play a significant role in symptom perception and reporting in patients with dyspeptic symptoms, and may play a role in ulcer formation.

## DIAGNOSIS OF PUD

### Clinical features

Clinically, PUD patients present with characteristic symptoms (Box 1).<sup>13</sup> Pain awakening the patient from sleep between 12 and 3 a.m. affects up to two-thirds of duodenal ulcer patients and one-third of gastric ulcer patients.<sup>27</sup> Older adults (>80 years old) with PUD have epigastric pain, nausea and vomiting as their most common presenting symptoms.<sup>27</sup>

#### BOX 1. Symptoms of PUD

- Epigastric discomfort
  - Specifically, pain relieved by food intake or antacids, and
  - Pain that causes awakening at night or that occurs between meals
- Loss of appetite
- Weight loss.

Source : Reference 13.

## Endoscopy

Essentially, the documentation of peptic ulcer disease depends on the utilization of endoscopy, which is the 'gold standard' as it can pick up superficial lesions, ulcer scars, as well as active ulcers<sup>28</sup>; in addition, multiple biopsies from gastric ulcers can be taken to look for malignancy, and antral biopsies can be obtained to test for *H. pylori* infection. Prompt endoscopy is particularly indicated in older patients and patients with alarm symptoms indicative of a possible complication or malignancy.<sup>13</sup>

## Tests for *H. pylori*

The diagnosis of *H. pylori* can be made based on endoscopic testing, via the rapid urease test, histology, smear cytology, or through non-invasive tests such as the C14 or C13 urea breath test or serum *H. pylori* serology.<sup>28</sup>

## TREATMENT APPROACH IN PUD

Effective management of recurrent PUD relies on identification and modification of treatable risk factors. Thus, looking for *H. pylori* infection, the overt or surreptitious use of NSAIDs and/or aspirin, and the possibility of an acid hypersecretory state are important diagnostic considerations in order to determine the optimal therapeutic approach, though the best treatment strategies for non-NSAID, non-*H. pylori*-associated peptic ulcers remain a challenge.<sup>5</sup>

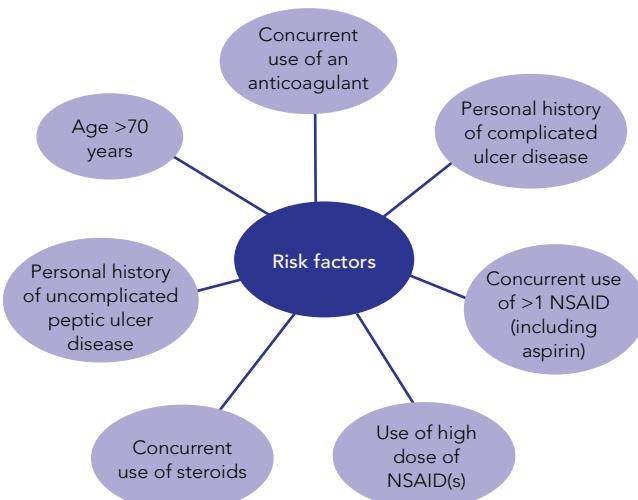
The available treatments for peptic ulcer are typically based on gastric acid suppression with antisecretory drugs and the eradication of *H. pylori* infection. Overall, a test-and-treat strategy, based on the results of *H. pylori* testing, is recommended for younger patients with no alarm symptoms – if *H. pylori* infection is diagnosed, it should be eradicated and antisecretory therapy [preferably with a proton pump inhibitor (PPI)] given for four weeks (see below).

Endoscopy referral is recommended for patients with persistent symptoms despite therapy.<sup>13</sup> For patients taking NSAIDs, this may help to triage the patients based on the individual's risk for complications seeing that the risk of developing a symptomatic ulcer varies considerably across patient profiles (Figure 6).<sup>29</sup> Regardless, those taking NSAIDs should discontinue their use if possible.

## PPIs such as rabeprazole

The gastric H<sup>+</sup>,K<sup>+</sup>-ATPase is the primary target for treatment of acid related diseases, and in fact bears the likelihood of being the most sustainable area of therapeutic application in the regulation of acid suppression<sup>30,31</sup>, a finding that has led to widespread use of these agents for such conditions. Pertinent comparative evidence applicable in PUD was provided in a randomized, double-blind, multicentre study, which compared the efficacy and tolerability of rabeprazole and omeprazole in patients with active duodenal ulcers, and found PPIs to be effective in healing active duodenal ulcer. In the study, where 102 patients with active duodenal ulcer received rabeprazole 20 mg and 103 patients omeprazole 20 mg once daily for 2 or 4 weeks, rabeprazole produced healing rates equivalent to omeprazole at weeks 2 and 4, and provided significantly greater improvement in daytime pain. After 2 weeks, complete ulcer healing was documented in 69% of patients given rabeprazole 20 mg and in 62% of patients given omeprazole 20 mg. After 4 weeks, healing

**FIGURE 6.** Risk factors for aspirin- and NSAIDs-associated ulcer complications

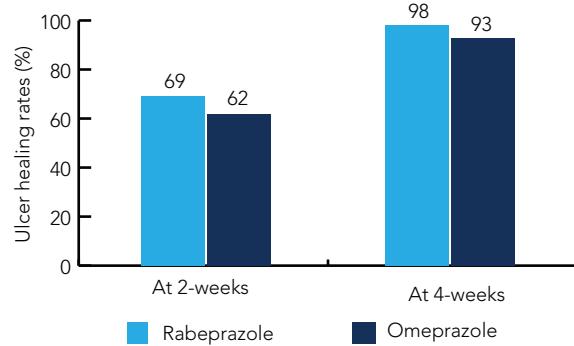


Source: Reference 29.

rates were 98% in the rabeprazole group and 93% in the omeprazole group ( $P = 0.083$ ) (Figure 7).<sup>32</sup> Importantly, at the study conclusion, rabeprazole-treated patients had significantly greater improvement in daytime pain symptom relief than those treated with omeprazole ( $P = 0.038$ ).

Of note, long-term PPI maintenance therapy may be required to prevent recurrent ulcer bleeding for patients with ulcer bleeding from *H. pylori*-negative, NSAID-negative ulcers, and for patients who require NSAID or aspirin maintenance therapy.<sup>16</sup>

**FIGURE 7.** Duodenal ulcer healing at 2 and 4 weeks of treatment with omeprazole 20 mg (n=103) and rabeprazole 20 mg (n=102)



Source: Reference 32.

## Regimens for *H. pylori* eradication

The eradication of *H. pylori* is a very important goal in the treatment of gastric and duodenal ulcers as it reduces the recurrence of PUD and is cost-effective.<sup>33</sup> An effective *H. pylori* eradication regimen should be based on local antibacterial resistance patterns; first-line agents for *H. pylori* eradication therapy include antisecretory therapy and combinations of antibiotics for 1-2 weeks.<sup>5</sup> PPI-based triple therapies for 7 days are also highly effective for the cure of *H. pylori*-positive peptic ulcers as well as for reducing ulcer recurrence [note: Huang et al<sup>34</sup> identified a pooled *H. pylori* eradication rate of 82.1% for PUD patients with the 7-d PCA (PPI, clarithromycin, amoxicillin) therapy].<sup>35</sup>

However, the standard triple eradication therapy may be replaced by quadruple therapy (PPI, bismuth, tetracycline, metronidazole).<sup>4</sup> This may be particularly important because antimicrobial resistance is increasing and traditional clarithromycin- or metronidazole-containing triple therapies may no longer be highly effective at eradicating the infection.<sup>36</sup> Here, combined bismuth- and metronidazole-containing quadruple therapy, or sequential 4-drug therapy, may be better choices for first-line treatment against this unique pathogen ideally suited to survive in the human stomach.

## Optimal management of PUD in the elderly

While the incidence of peptic ulcer is decreasing in the general population, the rates of hospitalization for gastric and duodenal ulcer remain very high in older patients, as is mortality from ulcer disease. Two factors that might explain this epidemiological feature in this patient population are the high prevalence of *H. pylori* infection and the increasing use of drugs that damage the gastrointestinal tract, including NSAIDs and/or aspirin (acetylsalicylic acid).<sup>35</sup>

As in all patients, the main goals for treating PUD in the elderly are to reduce disease recurrence and to prevent complications, mainly bleeding and perforation. However, the overall approach should include a comprehensive geriatric assessment in order to better define the clinical risk of adverse outcomes in these older patients with peptic ulcer and its complications.<sup>35</sup>

Antisecretory drugs are the treatment of choice for NSAID- or aspirin-related peptic ulcers, and are useful as preventive therapy in chronic users of NSAIDs and low-dose aspirin. Although these drugs are well-tolerated in geriatric patients, monitoring is suggested in older patients with frequent pulmonary infections, gastrointestinal malabsorption, unexplained chronic diarrhea, osteoporosis

or those taking concomitant cytochrome P450 2C19-metabolized medications, as PPIs may contribute to these conditions.<sup>35</sup>

## SURGICAL PERSPECTIVES IN PUD

Surgery had been the treatment of PUD for much of the 20<sup>th</sup> century. However, our improved understanding of ulcer pathophysiology paralleled the development of potent pharmacologic therapy, and thus patients failing medical therapy and requiring surgery became rare. In fact, the recognition of *H. pylori* infection as a cause of PUD, medical regimens to eradicate the organism, and the widespread use of PPIs to suppress gastric acid secretion has revolutionized the management of PUD, and has largely supplanted the need for gastric surgery for ulcer disease.

Surgery in PUD is generally reserved for the complications of the disease or for the rare case of refractory disease<sup>37</sup>; currently, bleeding is the most common indication for surgery. Often endoscopic therapy in conjunction with PPI administration controls most ulcer bleeding (see below), though other complications, such as perforation and gastric outlet obstruction, are rare but serious. In particular, peritonitis due to perforation is a surgical emergency that requires patient resuscitation; laparotomy and peritoneal toilet, omental patch placement and, in selected patients, surgery for ulcer control.<sup>13</sup>

Assuch, emergentsurgery for complicated peptic ulcers has not declined, though the development of PPIs and a full understanding of the impact of *H. pylori* have led to a trend towards minimalism even in surgical therapy for complicated PUD. New operations such as parietal cell vagotomy were developed to minimize the complications of surgery.<sup>38</sup>

## Endoscopic management of peptic ulcer bleeding

Peptic ulcer disease is the most common cause of upper gastrointestinal bleeding, where appropriate resuscitation followed by early endoscopy for diagnosis and treatment are of major importance. Endoscopy is recommended within 24 hour of presentation, and therapy is indicated for patients with high-risk endoscopic stigmata, particularly those with active bleeding and visible vessels.<sup>39</sup> High dose PPIs should be administered intravenously for 72 hour after endoscopy in high-risk patients; whilst *H. pylori* should be tested for in all patients with peptic ulcer bleeding and eradicated if positive.

## Laparoscopic repair for perforated PUD

Perforation also represents one of the most common complications of PUD, yet, in general, there is no consensus on treatment of this condition. For conservative treatment

there are only a few indications; use of an omental patch is recommended, while irrigation and drainage are not.<sup>40</sup>

The development of laparoscopic surgery has changed the way to treat such abdominal surgical emergencies, with some clinical trials suggesting that laparoscopic surgery could be a better strategy than open surgery in the correction of perforated peptic ulcer. However, the evidence is not strongly in favor for or against this intervention.<sup>40</sup> It is assumed that a decrease in septic abdominal complications may exist when laparoscopic surgery is used to correct perforated peptic ulcer.<sup>41</sup> Nonetheless, with the information provided it could be said that laparoscopic surgery results are not clinically different from those of open surgery.

## Evaluation and management of patients with recurrent PUD after acid-reducing operations

In patients with recurrent ulcer disease after acid-reducing operations, a relationship between ulcer recurrence and incomplete vagotomy has been suggested. The evidence that NSAID use is an important pathogenic factor in recurrent ulcer disease includes the relationship between NSAIDs and primary PUD, the occurrence of NSAID-induced ulcers in patients taking PPIs, and the demonstration of ulcer disease in patients taking aspirin despite prior acid-reducing operations. The relationship between *H. pylori* infection and postoperative ulcer recurrence remains uncertain despite documented high rates of *H. pylori* infection in postoperative patients.<sup>42</sup>

The initial management of patients with recurrent ulcer disease after acid-reducing operations consists of an antisecretory medicine, like PPIs, and antibiotics directed at *H. pylori*, if present; initiation of antibiotic therapy in presence of *H. pylori* infection is strongly supported by the critical role that it plays in primary PUD together with the minimal risks associated with *H. pylori* eradication.<sup>42</sup> Often, the principal indication for operative management of recurrent PUD, after failed acid-reducing operations, is the occurrence of ulcer complications, which cannot be managed by medical or endoscopic means.<sup>42</sup>

## COMPLICATIONS OF PUD

Besides the two major complications of PUD mentioned above (i.e., bleeding and perforation), there are two other similarly important complications, i.e., penetration; and obstruction.<sup>43</sup> All these complications can occur in patients with peptic ulcer of any etiology. However, it is important to consider that despite improvements in the medical management and the lower overall incidence of PUD, conflicting data exists about the incidence of potentially

life-threatening ulcer complications. In this regard, there are important time trends embedded within this stable overall rate of complications: the dramatic decline in the prevalence of *H. pylori*; an increased use of NSAIDs, and an increased rate of ulcer complications related to such drug use, especially in the elderly.

Because of these time trends, ulcer complications are on the rise in the elderly but on the decline in younger individuals. Hemorrhage is the most frequent PUD complication, the incidence of which is increasing in comparison to perforation and pyloric stenosis. As mentioned above, therapeutic endoscopy is a treatment of choice in this setting of bleeding ulcers and reduces the need for emergent surgical procedures to 10-20% of the cases. As well, the success of angiographic embolization in the containment of massive hemorrhage must also be considered. In addition, transcatheter arterial embolization is also a safe and effective treatment in patients with duodenal ulcers re-bleeding after therapeutic endoscopy or surgery.

## Relevance of potent gastric acid inhibition in the treatment of peptic ulcer hemorrhage

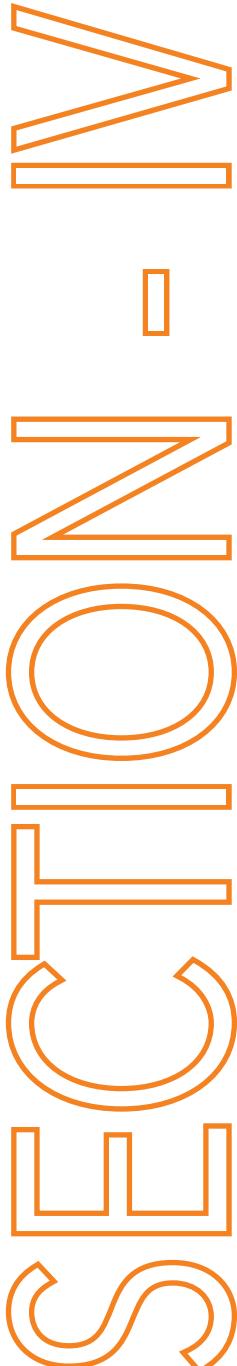
Upper gastrointestinal bleeding from PUD is a common clinical event, resulting in considerable patient morbidity and significant healthcare costs. In this setting, inhibition of the gastric acid secretion is a key component in improving clinical outcomes, including reduction in re-bleeding, transfusion requirements, and surgery, given that raising intragastric pH promotes clot stability and reduces the influences of gastric acid and pepsin. While patients with high-risk stigmata for ulcer bleeding (arterial bleeding, non-bleeding visible vessels, and adherent clots) benefit significantly from, and should receive, high-dose intravenous PPIs after successful endoscopic hemostasis, for patients with low-risk stigmata (flat spots or clean ulcer base), oral PPI therapy alone may be sufficient.<sup>44</sup> For oozing bleeding, which represents an intermediate-risk finding, successful endoscopic hemostasis and oral PPI are recommended. High-dose oral PPIs may be as effective as intravenous infusion in achieving positive clinical outcomes, though this is yet to be documented by randomized studies.

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# OTHER ACID RELATED DISORDERS



## THE ACIDIC EVENTS CONTINUE

In this last section, we cover other acid peptic disorders, distinct from gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD), which should be in the differential diagnosis of acid related disorders. As upper gastrointestinal symptoms occur in up to 40% of the population, an accurate diagnosis is essential to provide rational investigation and treatment.<sup>1</sup>

### DYSPEPSIA OR “DIFFICULT DIGESTION”

Difficult digestion is probably the most common presentation in clinical practice, distinguished by the medical name of “dyspepsia”, and consisting of an assortment of symptoms in the upper abdomen.<sup>2-5</sup> By itself, it is a major healthcare concern due to its prevalence, which is as high as 40% in the general population<sup>6</sup>, its impact on quality-of-life, and the associated significant health resource utilization.<sup>7</sup> Approximately 1/3<sup>rd</sup> of patients visiting general physicians have the dyspepsia syndrome, as do roughly 50% of those who visit gastroenterologists.<sup>8</sup> While reported consultation rates range from 5.4% to 56% for GERD, rates range from 26% to 70% in dyspepsia.<sup>9</sup>

#### Characterization of dyspepsia

Intrinsically, dyspepsia can be divided into two principal categories: “organic” and “functional”. Organic causes of dyspepsia are GERD and peptic ulcer (discussed in section 2 and 3), gastric or esophageal cancer, pancreatic or biliary disorders, intolerance to food or drugs, and other infectious or systemic diseases.<sup>2</sup> This should be distinguished from functional (non-ulcer) dyspepsia, which is characterized by symptoms without an underlying organic disorder.<sup>10</sup> Here, risk factors for functional dyspepsia have been shown to include female gender and underlying psychological disturbances, whilst environmental/lifestyle habits such as poor socio-economic status, smoking, increased caffeine intake and ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) appear to be more relevant to uninvestigated dyspepsia.<sup>11</sup>

#### Symptom presentation

The term “dyspepsia” per se is not a diagnosis but stands for a constellation of symptoms referable to the upper gastrointestinal tract (Figure 1).<sup>12,13</sup> These symptoms may coexist with symptoms of other functional gastrointestinal disorders such as functional heartburn and irritable bowel syndrome (IBS), and anxiety and depression. The history and physical examination can help identify other possible causes of dyspeptic symptoms.

### Dyspepsia and drugs (NSAIDs)

The etiology of dyspeptic symptoms is heterogeneous.<sup>(i)</sup> Regarding drug-induced symptoms, conventional non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid and cyclooxygenase-2 (COX-2)-selective inhibitors can all cause dyspepsia.<sup>(ii)</sup> Ofman et al<sup>(iii)</sup> sought to determine the risk of dyspepsia associated with NSAIDs, and found clinical trial data indicating a 3-fold increase in the risk of dyspepsia with high dosages of any NSAID, along with any dosage of indomethacin, meclofenamate, or piroxicam. Other NSAIDs at lower dosages were not associated with an increased risk of dyspepsia.

**Source:**

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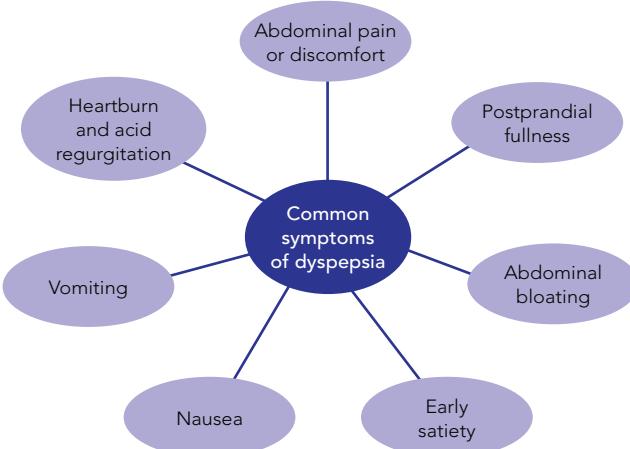
## Functional dyspepsia and GERD

An overlap between functional dyspepsia and GERD can be particularly confusing with respect to symptom presentation. Yet, while substantial groups of patients are without a definite structural or biochemical cause for their symptoms, and are considered to be suffering from functional dyspepsia, patients with heartburn and acid regurgitation invariably have GERD, and should be distinguished from those with dyspepsia.<sup>12</sup> Despite this, GERD and dyspepsia may occur simultaneously in an individual and therefore they may be difficult to discriminate.<sup>8</sup> In effect, a correlation exists between dyspepsia syndrome and GERD, particularly between the functional dyspepsia and non-erosive GERD (i.e., NERD).<sup>8</sup> Emerging evidence suggests that NERD is also a heterogeneous disorder, with some demonstrating abnormal acid exposure and/or sensitivity and others entirely normal 24-hour pH studies (functional heartburn). As follows, it would appear that the overlap of these two conditions is most apparent between functional dyspepsia and those NERD patients with normal pH studies.<sup>14</sup>

## Subtyping functional dyspepsia

Given the uncertain pathogenetic mechanisms, variable management, and often-ineffective medical therapy, functional dyspepsia remains a puzzling medical problem.<sup>15</sup> It is a highly prevalent and heterogeneous disorder<sup>16</sup>, which can be categorized into different subgroups based on the predominant symptom identified by the patient, and this subgroup classification can assist in deciding the appropriate symptomatic treatment for the individual patient.<sup>12</sup>

**FIGURE 1.** Common symptoms that present in variable combinations in patients with dyspepsia



Source: References 12,13.

**The ROME criteria:** The ROME III criteria address and define two distinct syndromes of functional dyspepsia: epigastric pain syndrome (characterized by pain and burning), and postprandial distress syndrome (characterized by meal-related symptoms).<sup>17-19</sup> The criteria state that one or more of four cardinal symptoms (Table 1) must be present within the previous 3 months, with symptom onset at least 6 months prior to diagnosis.<sup>13,20,21</sup> Importantly, symptoms of epigastric pain or discomfort have a prevalence of 89-90% in functional dyspepsia, with a similar prevalence

**TABLE 1.** Rome III diagnostic criteria for functional dyspepsia

### FUNCTIONAL DYSPEPSIA

**Diagnostic criteria\* must include:**

≥ 1 of the following:

- I. Bothersome postprandial fullness
- II. Early satiation
- III. Epigastric pain
- IV. Epigastric burning

AND

No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

\* Criteria fulfilled for the last 3 months, with symptom onset at least 6 months prior to diagnosis.

Source: References 13,20,21.

Please see highlights of ROME IV criteria for functional dyspepsia in the "Updates Section"

for postprandial fullness (75-88%), and early satiety (50-82%).<sup>22</sup>

## PATOPHYSIOLOGY – novel mechanisms in functional dyspepsia

The complex etiology of dyspeptic symptoms has opened a wide spectrum of putative mechanisms (Figure 2).<sup>2,5,23-29</sup> Several studies have shown potential associations between specific pathophysiologic disturbances and dyspeptic symptoms. Delayed gastric emptying is reported in about 30% of patients with functional dyspepsia and is associated with the symptoms of postprandial fullness, nausea, and vomiting. In contrast, impaired gastric accommodation, present in 40% of functional dyspepsia patients, is found to be associated with early satiety.<sup>30</sup> Hypersensitivity to gastric distension, observed in 37% of functional dyspepsia patients, is associated with the symptoms of postprandial pain, belching, and weight loss. Additionally, psychosocial factors and altered response to duodenal lipids or acid have also been identified as pathophysiologic mechanisms.<sup>31</sup>

Food and dietary habits may also contribute to the induction and/or exacerbation of dyspeptic symptoms given that dietary assessments have frequently implicated fatty foods in symptom induction.<sup>32</sup>

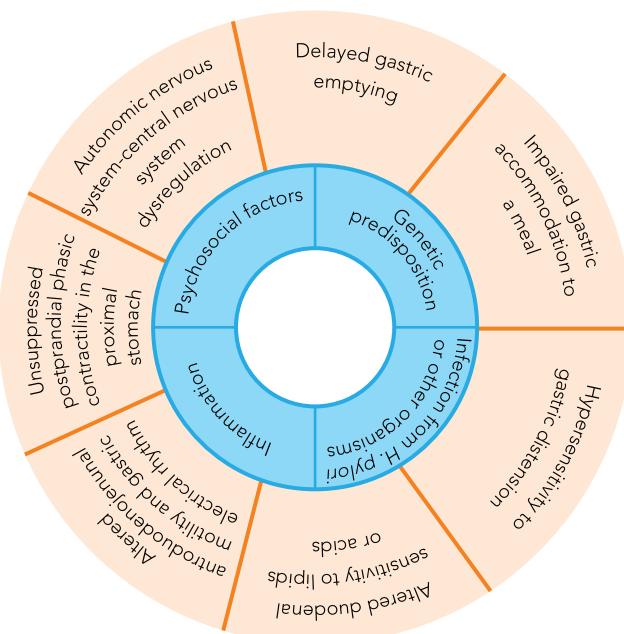
Ghrelin, a gut hormone that has an important role in gut motility, may also be associated with functional dyspepsia through its effect on the regulation of gut motility, though further studies are needed to examine the effects of ghrelin in functional dyspepsia.<sup>26</sup>

## Management of the patient with dyspepsia

The optimal diagnostic approach to the dyspeptic patient is a matter of debate given its functional nature and the multitude of possible pathophysiologic mechanisms. Thus, as no single treatment may be curative, reassurance of patients by ruling out more serious diagnoses, explanation of the disease process, and general advice pertaining to the underlying causes and dietary and life-style measures, are all important components of the management of these patients. Removing precipitating causes, such as medications, food or psychological factors/stress contributing to symptoms, is mandatory. Even so, well-established medical treatments include eradication of *Helicobacter pylori* (*H. pylori*) and the use of acid inhibitory agents or prokinetics.<sup>33,34</sup>

In general, extensive diagnostic testing (Box 1)<sup>2</sup> is not recommended in patients with non-ulcer dyspepsia, except in cases with serious risk factors for organic disease, such as dysphagia, protracted vomiting, anorexia, melena, anemia, or a palpable abdominal mass, wherein endoscopy should be considered to exclude GERD, peptic or duodenal

**FIGURE 2.** Pathophysiological mechanisms underlying functional dyspepsia



Inner circle shows pathogenetic factors implicated in functional dyspepsia.  
Outer circle shows pathophysiological mechanisms underlying functional dyspepsia.

Source: References 2,5,23-29.

ulcer, and gastric cancer.<sup>35</sup> Overall, before starting medical treatment for functional dyspepsia, a careful history and physical examination should exclude presence of 'alarm symptoms'.

Prompt endoscopy is imperative in all patients with alarm symptoms (including the first appearance of symptoms after the age of 50-55)<sup>36</sup> to detect any structural abnormality such as cancer, peptic ulcer or esophagitis.<sup>20</sup> In patients without these features, endoscopy is unlikely to contribute to medical management. In this latter group, a 'test and treat' strategy implying non-invasive testing for *H. pylori* and treatment of the infection if present seems to be a reasonable approach.<sup>37</sup>

### BOX 1. Diagnostic evaluation of dyspepsia may include

- Upper gastrointestinal endoscopy
- Abdominal USG
- Gastric emptying testing (scintigraphy, breath test, USG, or MRI)
- Gastric accommodation evaluation, [MRI, USG, single-photon emission computed tomography, and barostat].

USG - ultrasonography; MRI - magnetic resonance imaging.

Source: Reference 2.

Though the role of *H. pylori* in functional dyspepsia is a matter of debate, emerging data indicate a modest but clear benefit for the eradication of *H. pylori*, with improvement in dyspeptic symptoms in subgroup of patients with functional dyspepsia.<sup>38,40</sup> As such, eradication of *H. pylori* will reduce the risk to the patient with dyspepsia of developing a peptic ulcer, reduce the complication rate if prescribed NSAIDs, and later reduce the risk of gastric cancer.<sup>5</sup>

Pertinent to this strategy, the accuracy of non-invasive *H. pylori* testing needs to be high, and urea breath tests are preferred, with fecal antigen testing being a reasonable alternative.<sup>41</sup> Such non-invasive testing for *H. pylori*, however, loses its significance if the prevalence of *H. pylori* in the population is low, and empirical treatment with an antisecretory drug becomes a rational first step.

Thus, for uninvestigated dyspepsia in patients without alarm features, 'test and treat' is the preferred initial management method in areas with relatively high prevalence of *H. pylori*/PUD, while empiric antisecretory therapy is preferred in other parts of the world where the prevalence of *H. pylori*/PUD is relatively low.<sup>7</sup> Especially in Asia, *H. pylori* should not be overlooked when considering the pathophysiology of functional dyspepsia. This is supported by the results of a double-blind, randomized, placebo-controlled trial conducted in Singapore, which, in contrast to the prior results obtained in studies of Western populations, suggested that patients with functional dyspepsia could benefit from *H. pylori* eradication therapy, with as much as a 13-fold increase in the chance of symptom resolution.<sup>42</sup> It is therefore important that physicians involved in the care of dyspeptic patients be aware of the current *H. pylori* prevalence in their region.<sup>43</sup>

The recommended treatment for non-ulcer dyspepsia associated with *H. pylori* infection should be a 10-day course of treatment with a PPI and two antibiotics, and treatment efficacy should be assessed at least four weeks after completing treatment with a urea breath test or a stool antigen test.<sup>41</sup> Here it is important to reconsider that clarithromycin resistance has undermined traditional triple therapy in many regions so that it is no longer a suitable

choice as an empiric therapy (also see PUD section). Four-drug therapies, such as sequential, concomitant, and bismuth-containing quadruple therapy are generally acceptable choices as empiric therapies. Post-eradication testing is highly recommended to provide early identification of otherwise unrecognized antimicrobial resistance.<sup>44</sup>

Finally, if the patient is *H. pylori*-negative, or in cases of persistent symptoms after successful *H. pylori* eradication, empirical treatment with an antisecretory drug is justified.<sup>45</sup> Increasingly, this empirical acid inhibition strategy will probably be cost-effective as gastroesophageal reflux becomes the predominant disorder in dyspeptic patients.<sup>46</sup> In fact, empiric antisecretory therapy may generally be the preferred initial method of managing non-ulcer dyspepsia.<sup>7</sup> A PPI is superior to the use of H<sub>2</sub>-receptor antagonists in the initial treatment of *H. pylori*-negative dyspepsia patients.<sup>47</sup>

Further therapeutic strategies include the use of prokinetics, psycho-/neurotropic drugs as well as additional psycho- or hypnotherapy, given that overall treatment of non-ulcer dyspepsia can be challenging and the physician needs to balance medical management strategies with treatments for psychologic or functional disease.<sup>13,17,22</sup> Studies have also shown that non-ulcer dyspepsia patients have higher scores of anxiety, depression, neuroticism, chronic tension, hostility, hypochondriasis and tendency to be more pessimistic when compared with the community controls.<sup>48</sup> Thus, psychotropic agents should be used in patients with comorbid anxiety or depression.

It has been reported that therapy with PPIs yields benefits, especially in those patients with regurgitation and epigastric burning sensation, while prokinetic agents with no extrapyramidal side effects (such as domperidone and itopride) alleviate satiation, bloating and nausea by accelerating the slow gastric emptying. Second-line drugs with encouraging results in clinical trials, which can be used in functional dyspepsia, are low-dose tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).<sup>20</sup> Currently, there is insufficient evidence to confirm the efficacy of psychological intervention in non-ulcer dyspepsia.<sup>49,50</sup>

## ZOLLINGER ELLISON SYNDROME (ZES) – A GASTRIC ACID HYPERSECRETOORY STATE

Even though gastric acid secretion is infrequently measured in practice, it is important to recognize the possible role of gastric hypersecretion in patients with symptoms of acid-peptic disease, as they share several features of pathogenesis and treatment. Gastric acid hypersecretory states are characterized by basal hypersecretion of gastric

acid, and traditionally include disorders associated with hypergastrinemia (Table 2)<sup>51</sup>, hyperhistaminemia, and those of unknown etiology. Of these, Zollinger-Ellison syndrome (ZES), a rare disorder caused by tumor secretion of the hormone gastrin, has greatest degree of acid hypersecretion.<sup>52</sup>

**TABLE 2.** Causes of hypergastrinemia

Acidic gastric pH	Elevated gastric pH
1. Gastrinoma (sporadic ZES or associated with MEN type-1 syndrome)	1. Chronic atrophic gastritis associated with pernicious anemia
2. Antral-predominant <i>H. pylori</i> gastritis	2. Chronic atrophic gastritis associated with chronic <i>H. pylori</i> infection
3. Pyloric obstruction	3. Proton pump inhibitor therapy
4. Renal failure and uremia	4. H2 receptor antagonist therapy
5. Post gastric resection with intact antrum	5. Post-vagotomy

Source: Reference 51.

Interestingly, the odyssey of ZES began with the initial recognition of two patients with severe PUD in 1955 that spurred an international dialogue on this unique disease, ultimately culminating in the discovery that gastrin was the hormone secreted by pancreatic and duodenal tumors in these patients.<sup>53</sup>

The syndrome is characterized by refractory peptic ulcer disease, peptic ulcers of the upper gastrointestinal tract failing to heal despite maximal medical therapy, severe diarrhea, symptomatic GERD, and gastric acid hypersecretion associated with an islet-cell tumor of the pancreas or duodenum (gastrinoma).<sup>54</sup> Of note, ZES is sporadic in 62-80% of cases, while in 20-38% of cases it is associated with multiple endocrine neoplasia type 1 (MEN 1).<sup>55</sup>

### Characteristic localization of gastrinomas

It is observed that more than 80% of gastrinomas are localized in a specific anatomic area, the so called "triangle of gastrinomas", which is bordered by the convergence of the cystic duct and the common bile duct, the junction of the 2<sup>nd</sup> and 3<sup>rd</sup> portion of the duodenum, and the junction of the head and body of the pancreas.<sup>56</sup> Regarding origin, most gastrinomas arise from the duodenum (approximately 75%), whereas they are localized in the pancreas in 25% of cases. Occasionally, gastrinomas may occur in unusual sites like the ovary, mesentery, liver, bile duct, gastric antrum/pyloric area, renal capsule, and in the jejunum.

### Diagnosis of ZES – strategies to determine the causes of hypergastrinemia

Most patients with ZES present primarily with abdominal pain (83%); however, in contrast to older reports, an increasing proportion have diarrhea (71%).<sup>52</sup> Nonetheless, despite general awareness of ZES by most physicians, the diagnosis is delayed for a mean of 5 years from its onset.<sup>57</sup> This may be due to the considerable overlap between the fasting serum gastrin concentrations found in ZES and various common conditions, such as *H. pylori* infection and the use of acid-suppressing medications. As a result, establishing the cause of hypergastrinemia in individual cases can sometimes be difficult. Yet, as gastrinomas may cause serious complications and be potentially life threatening, investigation of hypergastrinemic patients should particularly focus on confirming or refuting the diagnosis of ZES.<sup>51</sup> Box 2 displays situations where the diagnosis of ZES should be suspected.<sup>52</sup>

The main diagnostic features of ZES are hypergastrinemia and acid hypersecretion<sup>56</sup> – diagnosis is established when the plasma gastrin is >1000 pg/mL and the basal acid output is >15 mEq/h in patients with an intact stomach, >5 mEq/h in gastrectomized patients, or when the hypergastrinemia is associated with a gastric pH <2.<sup>55, 58</sup> However, in patients with borderline results, a provocation test (with secretin or calcium) may be required. In these situations, evidence suggests that the secretin test should be used first, with the calcium stimulation test only being used if there is still diagnostic uncertainty.<sup>51</sup>

Several imaging techniques have been proposed to identify the localization of the gastrinoma. Somatostatin receptor scintigraphy is the best study for preoperative localization, with results as good as all other imaging studies combined; it can localize the tumor in 80% of the cases, and identify gastrinomas even in anatomic sites other than pancreas and duodenum. Endoscopic ultrasonography can also be an effective modality, with a sensitivity as high as 79-93% and a specificity of 93%.<sup>54</sup>

### BOX 2. Situations where diagnosis of ZES should be suspected

- In any patient with PUD/GERD who is *H. pylori* negative
  - Refractory to treatment
  - Has a virulent ulcer/GERD course
  - Has ulcers in unusual locations or has recurrent ulcers
- With PUD/GERD with a family/personal history of endocrinopathies such as hyperparathyroidism which would suggest MEN 1/ZES
- In a patient with PUD/GERD with hypergastrinemia or prominent gastric folds on endoscopy which occur in up to 92% of all ZES patients.

Source: Reference 52.

Furthermore, a number of tumor markers in addition to serum gastrin, including chromogranin A, neuron-specific enolase, and subunits of chorionic gonadotropin, have been proposed for use in either the diagnosis of pancreatic endocrine tumors, or for assessment of tumor extent and growth.<sup>57</sup>

## Therapy for ZES

The principal therapeutic strategies in ZES are to control both the gastric acid hypersecretion and the growth of the neoplasia. Proton pump inhibitors (PPIs) are the most effective antisecretory drugs, which can be administered at high dosages with few drug-related adverse effects<sup>55,58</sup> and are in fact the drugs of choice for patients with ZES; their safety in the maintenance therapy has been proven both in short- and in long-term studies. The recommended adult oral starting dosage of rabeprazole, a PPI, for ZES is 60 mg once daily.<sup>59</sup>

Somatostatin analogues can be useful in reducing gastric acid hypersecretion and serum gastrin levels, and can contribute to treating the disease more effectively. In addition, owing to their anti-proliferative effect, they can be used in the treatment of liver metastases from the primary gastrinoma.<sup>55</sup> Chemotherapy, interferon, and embolization are indicated only in patients with malignant progressive disease, i.e. rapidly evolving tumors or in cases where the tumoral symptoms cannot be treated by other approaches.<sup>54</sup> Embolization and chemoembolization are effective in controlling clinical symptoms; however, they have not been reported to improve survival.<sup>55</sup>

## Surgical management of ZES

In ZES patients, the best therapeutic procedure is surgery, which can be curative; in fact, a successful initial operation is the key to success in the management of a patient with ZES.<sup>60</sup> Medical treatment can be the best palliative therapy and should be used, when possible, together with surgery, in a multimodal therapeutic approach.<sup>56</sup> In the past, surgeons in this domain were initially challenged by the complexity of the patients and the need to perform total gastrectomy to prevent death from complications of the severe ulcer disease. Later, after the discovery of PPIs, total gastrectomy was no longer needed, and the surgeon could focus on tumor removal added by radioimmunoassay for gastrin and new imaging modalities.<sup>53</sup>

The goals of surgical treatment for ZES differ between sporadic and MEN-1-related cases. All sporadic cases of ZES should be surgically explored even with negative imaging results due to the high likelihood of finding and removing a tumor for potential cure. Essentially, the operative technique should always include duodenotomy (opening the duodenum) and meticulous dissection of lymph nodes in the gastrinoma triangle, since duodenal primary tumors are often missed and lymph node primary tumors or metastases are common.<sup>61</sup> In contrast, surgery for MEN-1-related cases should be focused on prevention of metastatic disease, being recommended when pancreatic tumors are greater than 2 cm. The role of Whipple procedure, especially for MEN-1 cases, needs to be explored further. Laparoscopic and endoscopic treatments are more experimental, but may have a role.<sup>62</sup> Again, postoperative evaluation should include secretin testing for the reason that it is the most sensitive method to document cure and detect tumor recurrence.<sup>61</sup>

## GASTRITIS – A WIDE RANGING PHENOMENON

Gastritis is a broad term, often used to describe different conditions by clinicians, though recent classification strategies have led to more congruence between specialists. Its clinical importance lies in the fact that gastritis predisposes patients to more pronounced damage to the gastric mucosa, in particular PUD, and possibly atrophic gastritis, intestinal metaplasia and gastric malignancy.<sup>63</sup>

### Histology of gastritis

The histological evaluation of the gastric mucosa is mandatory for diagnosing and classifying gastritis.<sup>63</sup> The condition is distinguished into two main categories, i.e. non-atrophic and atrophic, the latter being defined as the loss of appropriate glands in the gastric mucosa. An

international group of pathologists [Operative Link for Gastritis Assessment (OLGA)] has proposed a system for reporting gastritis in terms of its stage (the OLGA Staging System), which places the histological phenotypes of gastritis on a scale of progressively increasing gastric cancer risk, from the lowest (Stage 0) to the highest (Stage IV).<sup>64</sup>

### Etiology of gastritis

There are several etiological types of gastritis, wherein each different etiology is related to different clinical manifestations and pathological features. The main etiologic factor for gastritis is infection with *H. pylori*<sup>63,65</sup>; which is closely associated with the development of chronic gastritis.<sup>66</sup> This might be particularly relevant for

### The virulence of *H. pylori* & the Indian paradox

Almost half of the world's population suffers from the *H. pylori* infection, but only some individuals develop gastric diseases with clinical symptoms. A possible reason for the phenomenon may be the different pathogenicity of infectious *H. pylori* strains (see PUD section). The presence of cytotoxin-associated gene A (*cagA*) and expression of vacuolating cytotoxin activity encoded by vacuolating cytotoxin gene A (*vacA*) are considered the two major virulence markers of *H. pylori*. Numerous coinfections with different *H. pylori* strains in peptic ulceration or chronic gastritis patients indicate the diversity of *H. pylori*.<sup>(i)</sup>

### The Indian paradox

The divergent clinical outcomes associated with *H. pylori* infection are largely influenced by the levels of cytokines in the gastric mucosa, which in turn are dependent on cytokine gene polymorphisms. Pro-inflammatory cytokine polymorphisms are strongly associated with severe histological changes in the gastric mucosa in Caucasian populations; however, high cytokine levels are not seen in the gastric mucosa in Indians in spite of *H. pylori* colonization. Interleukin-1beta (IL-1 $\beta$ ) is a potent pro-inflammatory cytokine, which causes partial clearance of the organism as well as hypochlorhydria. Corpus hypochlorhydria causes a persistent *H. pylori* colonization followed by development of gastric atrophy and later on carcinoma. A lack of association with a pro-inflammatory polymorphism suggests presence of low levels of IL-1 $\beta$  in the gastric mucosa. As follows, there is low clearance of the organism and a high incidence of duodenal ulceration attributable to hyperchlorhydria. Nonetheless, it is protective against the development of gastric carcinoma. This might explain the "Indian Paradox" of the apparent discrepancy of high degree of *H. pylori* colonization and a low incidence of gastric carcinoma in the Indian population.<sup>(ii)</sup>

#### Source:

- (i) Chen XJ, Yan J, Shen YF. *Chin Med J (Engl)*. 2005;118(6):460-7.
- (ii) Moorchung N, Srivastava AN, Gupta NK, et al. *Singapore Med J*. 2007;48(5):447-54.

prognosis since atrophic gastritis (resulting mainly from long-standing *H. pylori* infection) is a major risk factor for the onset of (intestinal type) gastric cancer; the extent and site of the atrophic changes correlate significantly with the cancer risk.<sup>64,67</sup>

In addition, certain other risk factors have also been identified for the occurrence of gastritis. For instance, studies have revealed that obesity is related to an increased prevalence of endoscopic and histologic gastritis.<sup>68</sup> Also, an association of obesity with gastric ulcers has been demonstrated. Here, adiponectin, a bioactive molecule released from visceral fat, could be a protective factor of endoscopic gastritis.

### Therapy for gastritis

Overall, a tailored and cost-effective approach is required in most cases for optimal outcomes. Primary prevention of NSAID-related gastropathy can be enhanced by better education for clinicians and patients, so that both proper prescriptions of gastroprotective agents and adherence to therapy will improve.<sup>63</sup> Pertinent to *H. pylori* eradication therapy, the emerging problem of antibiotic resistance requires an accurate knowledge of local eradication rates. Standard triple therapy should be abandoned in regions with high clarithromycin resistance; instead, sequential or quadruple therapy is best initial treatment (see PUD section also).<sup>63</sup>

## STRESS RELATED MUCOSAL INJURY

While gastric acid is a prerequisite for the development of the mucosal injury, mucosal defense factors that maintain the integrity of the gastric mucosal barrier are equally important.<sup>69</sup> The stomach possesses many cytoprotective mechanisms against stress ulceration, such as the gastric microcirculation, prostaglandins, mucus secretion, epithelial cell renewal, and muscle tone.<sup>70</sup> Despite this, stress-related mucosal damage (SRMD) of the upper gastrointestinal tract may be an important cause of upper gastrointestinal tract

hemorrhage in postoperative and critically ill patients in the intensive care setting<sup>70</sup>, though it is relatively uncommon with modern intensive care.

Stress, defined as an acute threat to homeostasis, has both short- and long-term effects on the function of the gastrointestinal tract.<sup>71</sup> Pertinent to this discussion, SRMD is identified as an erosive gastritis of unclear pathophysiology, which can occur rapidly after a severe insult such as trauma, surgery, sepsis or burns, being apparent in 75–100% of

critically ill patients within 24 hours of admission to an intensive care unit (ICU).<sup>72</sup>

### Etiopathogenesis, and prognosis

Splanchnic hypoperfusion, in general, is the underlying etiology of stress-related mucosal injury and bleeding.<sup>73</sup> Furthermore, the mortality rate associated with clinically significant stress-related mucosal bleeding is high. Respiratory failure requiring mechanical ventilation for more than 48 hours and coagulopathy are two strong, independent risk factors for bleeding.<sup>72,73</sup> Other risk factors for clinically important bleeding from SRMD include shock, severe burns, a prior history of gastrointestinal ulceration, and multiple organ failure.<sup>72</sup>

### Use of PPIs for gastric acid suppression in critical illness

Mucosal damage typically manifests as multiple superficial gastric lesions without perforation, and bleeding often

originates in superficial capillaries after the patient is admitted to the ICU. As follows, the key to reducing mortality from stress-related bleeding in critically ill patients is to prevent mucosal damage, and to provide adequate visceral perfusion.<sup>73</sup> Even so, gastrointestinal function should be taken into consideration before using enteral nutrition, and this should not be the sole stress ulcer prophylactic therapy.

Acid-suppression therapy should be used to raise the intragastric pH above 3.5, as this reduces the incidence of stress-related mucosal bleeding. PPIs are at least as effective, and may be more effective than histamine H<sub>2</sub>-receptor antagonists in achieving this pH goal and preventing bleeding.<sup>73</sup> In fact, PPIs have largely replaced H<sub>2</sub>-receptor antagonists in the treatment of many acid-related conditions, as they achieve a more rapid and sustained increase in gastric pH and are not associated with the rapid tachyphylaxis seen with H<sub>2</sub>-receptor antagonists; as a result, they are beginning to be used for the prophylaxis of SRMD in critically ill adults.<sup>72</sup>

## REBOUND HYPERSECRETION

Consistent with the high prevalence of acid-related disorders; the drugs inhibiting gastric acid secretion are widely used in practice. However, symptom relapse may be common after withdrawal of these drugs. Both experimental as well as clinical studies have demonstrated increased acid secretion after a period of treatment with either H<sub>2</sub>-receptor antagonists or PPIs, characteristically known as 'rebound hypersecretion'; the clinical consequences of this phenomenon are yet to be settled.<sup>74</sup>

Rebound acid hypersecretion generally lasts more than 8 weeks, but less than 26 weeks after long-term proton pump inhibition. Increased parietal cell mass, as well as enterochromaffin-like (ECL) cell mass and activity, has been suggested as mechanisms of hypersecretion, though their relative contribution is not fully understood.<sup>75</sup> Even so, the phenomenon is likely to reflect the distinct sequence of events as shown in Figure 3.<sup>74</sup>

**FIGURE 3.** Sequence of events in rebound hypersecretion



Source: Reference 74.

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# UPDATES

## UPDATES ON GERD, PEPTIC ULCER DISEASE, AND FUNCTIONAL DYSPEPSIA

Acid-peptic disorders are widely prevalent worldwide. Gastroesophageal reflux disease (GERD), in particular, is one of the most common manifestations of acid-peptic disorders, defined as “symptoms or complications resulting from the reflux of gastric content into the esophagus or beyond, into the oral cavity (including larynx) or lung.” It includes three primary phenotypic presentations; erosive esophagitis, non-erosive esophagitis, and Barrett’s esophagus. Heartburn with or without regurgitation are typical symptoms of GERD. Majority of patients presenting to the outpatient department with typical GERD symptoms are prescribed empirical proton pump inhibitor (PPI) therapy, without the need for diagnostic testing. However, those with alarm symptoms such as weight loss, anorexia, and upper gastrointestinal (GI) bleed are advised upper GI endoscopy, with additional diagnostic tests, such as catheter-based pH test, wireless pH capsule, and impedance-pH monitoring required in select indications to arrive at the underlying diagnosis.<sup>1</sup>

Peptic ulcer disease (PUD), another form of acid-peptic disorder, remains a major cause of morbidity and mortality worldwide; *Helicobacter pylori* (*H. pylori*) is commonly co-associated. Diagnosis of PUD can be challenging as about two-third of these patients are asymptomatic, remaining presenting with common GI symptoms including epigastric pain, often with associated dyspepsia, nausea, bloating, or

early satiety.<sup>2</sup> It is noteworthy that symptoms of PUD, when present, can provide vital clue to the type of ulcer disease. While patients with duodenal ulcers often report worsening of abdominal pain on an empty stomach and describe hunger or abdominal pain about 2-3 hours after meals or at night; those with gastric ulcers usually complain of nausea, vomiting, weight loss and postprandial abdominal pain. In the absence of alarm symptoms (weight loss, early satiety, GI bleeding, dysphagia or odynophagia) empirical therapy using anti-secretory agents can suffice. Since *H. pylori* is an important cause of PUD, a test-and-treat strategy utilizing a non-invasive *H. pylori* test such as stool antigen or urea breath test is recommended in patients < 55 years without alarm manifestations, those living in geographic regions where gastric cancer is uncommon and prevalence of *H. pylori* > 20%. In older patients and those with alarm symptoms, endoscopy is recommended to establish a diagnosis.<sup>3</sup>

Functional dyspepsia is a common functional GI disorder associated with impaired digestion, and which includes patients who fulfil criteria of postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS) in the absence of any structural disease that can explain these symptoms. All functional GI disorders are diagnosed and classified using the ROME criteria, which have been amended from time-to-time based on emergence of new scientific data. In the recent ROME IV section on functional dyspepsia (ROME IV criteria for functional GI disorders 2016), minor changes to the previous Rome III criteria were introduced with the aim to improve specificity of the definition of this disorder. The ROME IV criteria specify that among the major symptoms of functional dyspepsia, not only postprandial fullness, but also epigastric pain, epigastric burning, and early satiation should be “bothersome” symptoms (see ROME IV criteria for functional dyspepsia in the box). Functional dyspepsia continues to be subcategorized into PDS and EPS, although it was recognized that there can be significant overlap of symptoms in these two subcategories. In addition to postprandial fullness and early satiety that can occur after meals in PDS, epigastric pain or burning and nausea may also increase after meal ingestion. Therefore, the definition of PDS was slightly modified, with ROME IV criteria acknowledging that patients with PDS, in addition to postprandial fullness and early satiety, may also



**MAJORITY OF PATIENTS PRESENTING TO THE OUTPATIENT DEPARTMENT WITH TYPICAL GERD SYMPTOMS ARE PRESCRIBED EMPIRICAL PROTON PUMP INHIBITOR (PPI) THERAPY, WITHOUT THE NEED FOR DIAGNOSTIC TESTING**



## BOX: ROME IV CRITERIA FOR FUNCTIONAL DYSPEPSIA

### B1. Functional Dyspepsia

#### Diagnostic criteria

1. One or more of the following:
    - a. Bothersome postprandial fullness
    - b. Bothersome early satiation
    - c. Bothersome epigastric pain
    - d. Bothersome epigastric burning
- AND

2. No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

<sup>a</sup>Must fulfill criteria for B1a. PDS and/or B1b. EPS.

<sup>b</sup>Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

**Source:** For complete criteria of PDS and EPS as mentioned in ROME IV criteria, please visit: **1.** Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, Talley NJ: *Gastroduodenal disorders*. *Gastroenterology* 2016; 150: 1380–1392. **2.** Suzuki H. *J Neurogastroenterol Motil*. 2017 Jul 30;23(3):325-333.

experience epigastric pain and burning or modification of these symptoms after meal ingestion.<sup>4-6</sup> It is noteworthy that overlap of PDS and EPS is more frequently observed in the hospital-based population compared to the general population.<sup>5</sup> Additionally, bloating, belching, and nausea were recognized as overlap symptoms in PDS and EPS. Other common GI disorders, such as GERD and irritable bowel syndrome (IBS), often coexist with functional dyspepsia.<sup>4</sup>

## MANAGEMENT UPDATES

PPIs remain the front-line treatment option for acid-peptic disorders, with documented superiority over H2 receptor antagonists due to their superior inhibitory effect on gastric acid secretion.<sup>7,8</sup> They can more reliably maintain intragastric pH > 4 for between 15-21 hours daily compared to only 8 hours for H2 receptor antagonists; additionally they have proven benefits in better controlling postprandial and nocturnal intragastric pH. Currently available PPIs include omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. Dexlansoprazole is also approved by USFDA and available in many parts of the world. All currently-approved PPIs are benzimidazole derivatives. An imidazopyridine PPI, tenatoprazole has also undergone evaluation in clinical trials and is still not approved for clinical use. To improve drug delivery, PPIs are being currently marketed in novel delivery systems; recently, dual-release dexlansoprazole formulation is made available to release the drug in two separate pH-controlled phases.



**THE ROME IV CRITERIA SPECIFY THAT AMONG THE MAJOR SYMPTOMS OF FUNCTIONAL DYSPEPSIA, NOT ONLY POSTPRANDIAL FULLNESS, BUT ALSO EPIGASTRIC PAIN, EPIGASTRIC BURNING, AND EARLY SATIATION SHOULD BE "BOTHERSOME" SYMPTOMS**



Inclusion of gastric acid secretion stimulators along with the PPI can obviate requirement for pre-meal dosing.<sup>8</sup> However, despite their overall efficacy in the management of different acid-peptic disorders, PPIs have certain limitations. Adverse effects associated with their inappropriate and often long-term use, particularly in the elderly and in those with comorbidities, is a serious cause of concern.<sup>7</sup> Their long-term use may affect calcium, magnesium, and vitamin B12 absorption. Additionally, long-term PPI use may possibly increase susceptibility to different enteric infections, including small intestinal bacterial overgrowth and *Clostridium difficile* infection. Their use has also been linked to community-acquired pneumonia, although this association has not been unequivocally proven.<sup>8</sup>

## Advances in GERD management

There is good evidence to support superiority of PPIs over H2 receptor antagonists for symptom relief in both erosive esophagitis and non-erosive reflux disease. Over the last few years several treatment strategies have been proposed to improve response with PPI. Relative benefits of continuous PPI use over "on-demand" (intermittent) treatment are still being explored. Spreading the dose of PPI during the day appears to improve control of intragastric pH. In patients with persistence of symptoms despite twice-daily PPI dosing, addition of bedtime H2 receptor antagonist has shown some benefits in symptom control. Similarly, doubling the PPI dose in patients with difficult-to-control reflux symptoms is another treatment strategy associated with mixed results.<sup>1</sup> Add-on treatment with prokinetics, alginates, and transient lower esophageal sphincter relaxation inhibitors may also afford some improvement in select patients with refractory GERD. Neuromodulators, including antidepressants, may improve symptoms in patients in whom visceral hypersensitivity may be contributing to the perception of GERD symptoms.<sup>9</sup>

Vonoprazan, a recently introduced potassium-competitive acid blocker has shown improvement in many acid-related disorders including GERD and NSAID-induced peptic ulcers.<sup>10</sup> Baclofen appears promising in patients with refractory GERD and residual acid or weakly acid reflux. Surgical options are reserved for select candidates, including those with poor compliance or concerns about medical therapy; abnormal pH test despite maximum PPI dose; symptoms with a large hiatal hernia; and symptoms correlating with non-acid reflux despite maximum PPI dose. Over the last few years, different forms of minimally-invasive endoluminal surgical procedures have been described that interfere with the mechanism of GERD. Many of these procedures are less invasive and safer than surgical fundoplication.<sup>1</sup>

### Advances in PUD management

Prior to the discovery of *H. pylori*, acid-suppressive therapies were primarily used for PUD management, based on the age-old dictum “no acid- no ulcer”. In these patients, PPIs, H2 receptor antagonists, and prostaglandin analogues (misoprostol) were widely used and continue to be used with success for prevention of PUD. Risk factor management (stop smoking and alcohol abuse, and avoid NSAIDs) along with effective management of complications, such as ulcer bleeding is part of the comprehensive management approach in these patients. The standard first-line treatment of *H. pylori* includes triple therapy, utilizing PPI in combination with two antibiotics (clarithromycin and amoxicillin or metronidazole) administered for 7-14 days; or quadruple therapy with bismuth/tetracycline. Rising resistance rates of *H. pylori* to many of these antibiotics, though, is a cause of growing concern.<sup>11</sup> Vonoprazan is also effective in many patients.<sup>10</sup> Recently, monoterpenes, a class of terpenes, have been proposed as potential therapies in difficult-to-treat cases based on their anti-ulcerogenic, healing, and antimicrobial effects, although these benefits have only been currently shown in experimental models.<sup>11</sup>

### Advances in functional dyspepsia management

Both PPIs and H2 receptor antagonists continue to be effective in the treatment of functional dyspepsia, though definitive benefits of PPI appear to be limited to EPS without much improvement in symptoms of PDS.<sup>5,12</sup> There is good data on prokinetics in these patients since motility disorders may be a possible underlying cause of functional dyspepsia, although the prototypic drugs of this class (cisapride and domperidone) are not available in many



**BOTH PPIs AND H2 RECEPTOR ANTAGONISTS CONTINUE TO BE EFFECTIVE IN THE TREATMENT OF FUNCTIONAL DYSPEPSIA, THOUGH DEFINITIVE BENEFITS OF PPI APPEAR TO BE LIMITED TO EPS WITHOUT MUCH IMPROVEMENT IN SYMPTOMS OF PDS**



parts of the world.<sup>5</sup> Itopride and levosulpiride appears promising.<sup>12</sup> Prucalopride, a selective 5-HT4 agonist, is effective in functional dyspepsia when the indication for treatment is refractory obstipation, though the drug is still not approved in this indication. Surprisingly, *H. pylori* eradication therapy has shown improvement of symptoms in a subset of patients with functional dyspepsia, prompting suggestions that *H. pylori*-associated dyspepsia may be a subgroup of functional dyspepsia. However, this is not currently proven.<sup>12</sup> Antidepressant drugs may be used in patients who fail to respond to first-line drugs.<sup>5,12</sup> Other therapies such as buspirone, acetamide, and tandospirone are being evaluated in these patients.<sup>5</sup> Phytotherapy and complementary treatment options have also been tried in these patients with some success.<sup>12</sup>

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## SELECT EXTRACTS FROM – WORLD GASTROENTEROLOGY ORGANISATION GLOBAL GUIDELINES: GERD GLOBAL PERSPECTIVE ON GASTROESOPHAGEAL REFLUX DISEASE – 2017

### Diagnosis

- Presence of heartburn and/or regurgitation symptoms ≥ 2 times/week is suggestive of GERD
- Initial evaluation of GERD should include documentation of the presence, severity, and frequency of heartburn, regurgitation, and alarm features; additional atypical symptoms (esophageal, pulmonary, otorhinolaryngological, and oral) should also be sought
- An empirical high-dose, short-course (1-2 weeks) of PPI therapy ("PPI trial") is not necessary to determine whether or not the patient's symptoms are acid-related, though this strategy is commonly practiced
- In patients refractory to PPI treatment, ambulatory 24-hour esophageal pH/impedance monitoring, with the patient off PPI therapy, may be considered to help characterize symptoms
- Esophageal pH or pH-impedance monitoring and esophageal manometry, although safe, are seldom required in the routine diagnostic algorithm of GERD. Intractable reflux symptoms or GERD complications can be evaluated safely using esophagogastric duodenoscopy (EGD)

### Management

- For patients with mild symptoms, and in some patients with non-esophageal reflux disease (NERD), self-directed, intermittent PPI therapy ("on-demand therapy") may be useful
- At the primary care level, PPIs or a combination of alginate-antacid and acid-suppressive therapy can be prescribed at the physician's discretion, which may be more beneficial than acid-suppressive therapy alone
- Optimal PPI therapy may be defined as taking the PPI 30-60 minutes before breakfast, and in the case of twice-daily dosing, 30-60 minutes before the last meal of the day as well
- Patients in whom full-dose PPI treatment fails, with or without adjuvant therapies, may benefit from a trial of step-up therapy to a twice-daily PPI regimen
- Treatment options for family physicians (Reinforce lifestyle modifications; endorse OTC medications [antacids and alginates, H<sub>2</sub> receptor antagonists] as appropriate; prescription H<sub>2</sub> receptor antagonists; PPIs; Prokinetics [few prokinetics are available for clinical use; their efficacy at best modest in GERD; not recommended]).

**Sources:** Hunt R, Armstrong D, Katelaris P, Afihene M, Bane A, Bhatia S, Chen MH, Choi MG, Melo AC, Fock KM, Ford A, Hongo M, Khan A, Lazebnik L, Lindberg G, Lizarzabal M, Myint T, Moraes-Filho JP, Salis G, Lin JT, Vaidya R, Abdo A, LeMair A; Review Team: World Gastroenterology Organisation Global Guidelines: GERD Global Perspective on Gastroesophageal Reflux Disease. *J Clin Gastroenterol.* 2017 Jul;51(6):467-478. doi: 10.1097/MCG.0000000000000854.

