

# Dyspepsia: literature review and evidence for management in primary care

M Torlutter, SC Onwukwe, D Pretorius, NM Mpangula, OB Omole

Division of Family Medicine, Department of Family medicine, University of the Witwatersrand, Johannesburg, South Africa

\*Corresponding author, email: [alagbaomole@gmail.com](mailto:alagbaomole@gmail.com)

## Abstract

Dyspepsia is a common reason for the clinical encounters in primary care. Two common causes of dyspepsia are gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD). These diseases clinically overlap and may present diagnostic and management challenges in primary care, especially in low resource settings. Proton pump inhibitors, eradication of *H. pylori* infection and endoscopy form the backbone of management of both diseases. This article reviews current considerations in the diagnosis and management of GERD and PUD in primary care.

**Keywords:** Dyspepsia, peptic ulcer, gastroesophageal reflux, primary care

## Introduction

Dyspepsia is a common reason for clinical encounter in primary care and imposes significant psychosocial stress, higher cost of care and lower quality of life on those who suffer from it.<sup>1-3</sup> It accounts for 5% of visits to family physicians in the US but data is not available for most African countries.<sup>4</sup>

There is no universally accepted definition for dyspepsia. Rather, dyspepsia refers to recurrent symptoms that alert the physician to a problem within the upper gastrointestinal tract. These symptoms include upper abdominal pain or discomfort, heartburn, and acid reflux. These symptoms are however non-specific, and alone should not be considered to identify dyspepsia.<sup>5</sup> The commonest causes of dyspepsia are: gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD). This article reviews important diagnostic and management considerations in these two common causes of dyspepsia and provides evidence-based management approaches for primary care physicians.

## Gastroesophageal reflux disease (GERD)

GERD is a common diagnosis in primary care and most people at one time of their life will suffer from it. Up to 10% of Americans experience daily heartburn and a third report periodic symptoms.<sup>6</sup> The American College of Physicians describe GERD as symptoms or complications resulting from the perceived reflux of gastric contents into the esophagus or hypopharynx.<sup>7</sup> There is huge variation in the global distribution of the disease, with higher prevalence in Western than Asian/African countries (25–40% vs < 5%).<sup>8-12</sup> Its incidence increases gradually with age and peaks after 40 years.<sup>10-11</sup> The male to female ratio is roughly 1:1 but this can vary widely in clinical subsets of GERD.<sup>9,11,13</sup> While white males are at increased risk of developing Barrett’s esophagus and adenocarcinoma,<sup>11</sup> nocturnal reflux symptoms are associated with greater damage to the esophagus.<sup>14-15</sup> Although it utilised a small sample size, a South African study has also found an association between non-acid GERD and squamous cell carcinoma of the esophagus.<sup>16</sup>

**Table 1:** Risk factors associated with GERD<sup>39</sup>

Strong associations	Weak associations
Family history of heartburn or GERD (3 times more likely to experience symptoms)	Drugs that reduce lower esophageal sphincter tone (nitrates, Calcium channel blockers (CCB), alpha/beta adrenergic agonists, theophylline, anticholinergics)
Risk increases with older age	Psychological stress
Hiatus hernia (decreased competence of gastroesophageal junction and poor clearance of esophageal acid post-reflux)	Asthma (asymptomatic GERD common in poorly controlled asthma, but PPIs not shown to improve asthma control)
Obesity	NSAIDs (not shown to cause GERD, but may contribute to esophagitis/strictures)
Pregnancy (progesterone relaxes lower esophageal sphincter)	Alcohol (evidence mixed, > 7 drinks per week may increase risk)
	Smoking
	Dietary factors (inconclusive and limited evidence regarding portion size and food types including fatty foods, caffeine, carbonated drinks, citrus, chocolate, spicy foods)

GERD results from three mechanisms<sup>17,18</sup>:

- Incompetent lower esophageal sphincter that allows backward movement of acidic gastric content into the esophagus and hypopharynx.
- Poor clearance of refluxed content from the esophagus. Though most people reflux, most do not develop GERD. The persistence of refluxed content is what results in chemical injury to the esophagus.
- Poor gastric emptying resulting in backward spilling of gastric content into the esophagus.

Risk factors for GERD are shown in Table 1.<sup>6</sup> However, the literature is not consistent in demonstrating associations with these risk factors.

**Clinical presentation**

Patients with GERD may present with or without symptoms of esophagitis and may have or not have endoscopic evidence

of reflux disease (erosive vs non-erosive). Clinical presentation may also overlap that of other gastrointestinal and pulmonary disorders, that are grouped into esophageal and extraesophageal symptoms – Table 2.

The most common symptoms are heartburn and regurgitation.<sup>19-20</sup> Less frequently, there may be non-cardiac chest pain and dysphagia.<sup>19,21</sup> A key diagnostic task is to exclude differential diagnoses like angina pectoris, peptic ulcer disease, other causes of esophagitis, asthma and chronic obstructive airway disease.<sup>20,22,23</sup> Patients may also present with complications such as ulceration, stricture, dental erosion, Barrett’s esophagus and adenocarcinoma of the esophagus – Table 3.<sup>24-27</sup> These conditions, though uncommon, confer appreciable morbidity and decrease in quality of life.<sup>10,19</sup> However, GERD carries minimal risk for mortality (estimated at 1 death per 100,000 patients per year) and most deaths arise from GERD-induced esophageal adenocarcinoma.<sup>10,28</sup>

**Table 2:** Signs/Symptoms and complications of GERD<sup>9,19-20,31</sup>

<b>Esophageal</b>	<b>Extra-Esophageal:</b>
<ul style="list-style-type: none"> <li>• Heartburn*</li> <li>• Regurgitation*</li> <li>• Chest pain</li> <li>• Dysphagia</li> <li>• Odynophagia</li> </ul>	<ul style="list-style-type: none"> <li>• Chronic cough</li> <li>• Wheezes</li> <li>• Aspiration Pneumonia</li> <li>• Sore throat</li> <li>• Halitosis</li> <li>• Hoarseness</li> <li>• Dental erosions</li> </ul>

\* = very common

**Complications of GERD** <sup>21,29-32</sup>

The America Gastroenterology Association classifies GERD according to the Montreal criteria:

Esophageal syndromes	
1. Syndromes with symptoms and no injury:	<ul style="list-style-type: none"> <li>• Typical reflux syndrome</li> <li>• Reflux chest pain syndrome.</li> </ul>
2. Syndromes with esophageal injury:	<ul style="list-style-type: none"> <li>• Reflux esophagitis</li> <li>• Reflux stricture</li> <li>• Barrett’s esophagus</li> <li>• Esophageal adenocarcinoma</li> </ul>
Extra-esophageal syndromes	
1. Established associations:	<ul style="list-style-type: none"> <li>• Reflux cough syndrome</li> <li>• Reflux laryngitis syndrome</li> <li>• Reflux asthma syndrome</li> <li>• Reflux dental erosion syndrome</li> </ul>
2. Proposed associations:	<ul style="list-style-type: none"> <li>• Pharyngitis</li> <li>• Sinusitis</li> <li>• Idiopathic pulmonary fibrosis</li> <li>• Recurrent otitis media</li> </ul>

**Table 3:** The differential diagnosis of GERD and PUD

Gastroesophageal reflux disease	Peptic ulcer disease
• Coronary artery disease	• Esophageal cancer
• Functional esophageal disorder/functional heartburn	• Stomach cancer
• Achalasia	• GERD
• Non-ulcer dyspepsia	• Gastroparesis
• Peptic ulcer disease	• Biliary colic
• Eosinophilic esophagitis	• Acute pancreatitis
• PPI-responsive esophageal eosinophilia	• Functional/non-ulcer dyspepsia
• Malignancy	• Coeliac disease
• Laryngopharyngeal reflux	• Irritable bowel syndrome
	• Pleuritic disease
	• Pericarditis

## Making a diagnosis<sup>17</sup>

GERD is a clinical diagnosis. A history of heartburn and/or regurgitation, with or without other symptoms or complications, are the key diagnostic features.<sup>17</sup> When heartburn and regurgitation are present together, diagnosis of GERD can be made with > 90% accuracy.<sup>19-20</sup> Relief of symptoms with empirical antacids or Proton pump inhibitors (PPI) is also diagnostic and confirmatory tests are not necessary.<sup>19-20</sup> However, failure to get relief does not exclude GERD. Heartburn is a perceived burning sensation under the sternum that is associated with meals, recumbency, nocturnal occurrence and is relieved by antacids.<sup>2,6</sup> Regurgitation is characterised by acid taste in the mouth and results from spontaneous return of gastric contents back into the esophagus or hypopharynx.<sup>9,19</sup>

Extra-esophageal syndromes (Table 2) are generally multifactorial and occur less commonly.<sup>21,29-32</sup> Red flag symptoms such as anaemia, dysphagia, haematemesis, melaena, persistent vomiting, or unintentional weight loss raise the possibility of esophagitis, stricture or cancer and should prompt immediate further investigation.

Physical examination is usually normal but may reveal extraesophageal signs - Table 2. Confirmatory tests for GERD are usually not required in patients with both heartburn and regurgitation. However, useful investigations include<sup>18,33</sup>:

- 1. Endoscopy:** may assist with diagnosis but is not routine. It is highly recommended for the diagnosis and surveillance of Barrett's esophagus (white males more at risk), excluding complications and other diagnoses – hiatus hernia, stricture, ulcers and cancer. In patients with longstanding symptoms suggestive of Barrett's esophagus, it may be better to perform endoscopy while on treatment.
  - 2. Barium imaging:** is rarely used, as endoscopy is of superior diagnostic value and provides direct visualisation and the opportunity for biopsy. However, barium swallow may be useful in patients with dysphagia, as a complement to endoscopy.
- If endoscopy is unrevealing and symptoms persist despite twice daily PPIs, further testing may be required, but guidelines differ as to the sequence. Further testing may include:
- 3. Manometry:** to evaluate esophageal contractions and lower esophageal sphincter function.
  - 4. Ambulatory reflux pH or impedance-pH monitoring:** where symptoms correlate with esophageal acid, and pH or impedance-pH testing to detect both acid and non-acid reflux events.
  - 5. Esophageal capsule endoscopy:** is a potential screening and diagnostic tool. It is less invasive and has moderate sensitivity and specificity.

Patients with GERD who have longstanding or relapsing symptoms, who are unresponsive to PPIs, who have red flag symptoms that suggest complicated disease (Table 2) require further investigations because up to 60% of GERD patients may

have minimal changes on white light endoscopy, narrow band imaging.<sup>34</sup>

Routine testing for *H. pylori* is not recommended by GERD guidelines, although eradicating *H. pylori* infection has been found to improve quality of life of patients with GERD, regardless of treatment outcome.<sup>35</sup>

## Differential diagnosis

Table 3 lists differential diagnoses of GERD. Uncommon symptoms, including dysphagia, bloating and early satiety, should raise concern about esophageal motility disorders, stricture, ring, or malignancy.

## Management

A management approach is summarised in the Figure 1. Lifestyle modification and acid suppression form the basis of treatment with most patients requiring prolonged therapy.

- **Lifestyle modification:** Advice should focus on healthy eating (avoiding coffee, chocolate and fatty foods), weight reduction, smoking cessation, avoiding alcohol, avoiding meals 3–4 hours before sleep and raising the head of the bed when sleeping. While there is evidence for weight reduction and elevation of the head of bed, routine food elimination is not recommended, as evidence for this is not robust or consistent across studies.<sup>36-37</sup>
- **Acid suppression:** Response to antacids or PPIs is often diagnostic of GERD.<sup>18</sup> Some evidence exists that on-demand PPI may not be inferior to continuous maintenance regimen.<sup>38</sup> Details of drug treatment and important considerations are shown in Figure 1. When drug treatment fails, or patient is unable to adhere to PPI treatment, surgical management may be considered. PPI treatment on a long term may be a risk for bone fractures, hypomagnesemia, community-acquired pneumonia and decrease efficacy of clopidogrel. Except for the last, robust data is lacking.<sup>39</sup>
- **Medication review:** For drugs that may aggravate dyspepsia, e.g. calcium antagonists, nitrates, theophyllines, bisphosphonates, corticosteroids and NSAIDs.
- **Surgical interventions<sup>39</sup>:** GERD patients who respond to PPIs are most likely to benefit from anti-reflux surgery. Patients who have non-acid reflux symptoms are less likely to respond to PPIs and may also benefit from anti-reflux surgery. Patients with Barrett's esophagus with low grade dysplasia may be amenable to fundoplication while those with high grade dysplasia may need ablation, mucosal resection or even esophagectomy. Patients with stricture may require repeated esophageal dilatation. Referral to a gastroenterology unit should also be considered if symptoms are unresponsive to treatment, in those who are young and require PPIs life-long, those non-adherent to PPIs and those with large or rolling hiatus hernia with obstructive symptoms.
- **Psychosocial support:** GERD is associated with various psychosocial factors which could decrease the quality of life. Chronic stress, anxiety and depression are common associations and are often considered risk factors for GERD.

Persons living with GERD may experience relational stress and even impairment at the workplace, and certain working conditions, such as night shift work and other life style factors, may also be risk factors for erosive esophagitis.<sup>40</sup> One of the big challenges marriage counsellors face when dealing with couples where one lives with GERD is the patient's self-awareness of halitosis or potential halitosis, as well as the partner's perception which can be accepting or not of the condition, especially with regard to its effects on intimate interactions. Halitosis in a patient with GERD is both a stomatological and psychological problem.<sup>41</sup> It is important that a biopsychosocial assessment is done to offer specialised psychosocial support to the patients who may need additional help.

**Peptic ulcer disease (PUD)**

PUD is a common cause of dyspepsia and has a lifetime prevalence between 8 and 14%.<sup>5</sup> While most PUD patients are in their active and productive years, most patients requiring admission for complications are older than 65 years. Table 3 shows the risk factors associated with PUD; the two commonest are H. pylori infection which is highly prevalent in South Africa (77.6%)<sup>42,43</sup> and the widespread use of NSAID.<sup>24,44</sup>

**Clinical presentation**

PUD most commonly presents with chronic or recurrent upper abdominal pain that may be related to meals and is often nocturnal.<sup>45</sup> The absence of pain, however, does not exclude the diagnosis, especially in the elderly and those on NSAIDS. Often, the only feature on physical examination is central epigastric tenderness, which is uncommonly experienced as 'pointing tenderness'. Less frequent presentations include severe pain radiating to the back in duodenal ulcers that penetrate posteriorly into the pancreas, or associated diarrhea in Zollinger-Ellison syndrome.<sup>45</sup> A minority present with complications such as upper gastrointestinal bleeding, intestinal perforation and gastric outlet obstruction (up to 15%, 7% and 3% of patients respectively).<sup>5</sup> Complications may occur without previous symptoms, especially in patients taking NSAIDS. Vomiting and early satiety should raise the suspicion of pyloric stenosis. Red-flag symptoms such as weight loss, anemia, vomiting, early satiety, dysphagia and age > 50 years should raise the

possibility of upper gastrointestinal cancer and require referral for endoscopy and biopsy.<sup>24,46</sup>

**Making a diagnosis**

Apart from obtaining a positive history of NSAID use, PUD can be made in a person with upper abdominal pain by:

**1. Endoscopy:** This is the gold standard test, being more sensitive and specific for PUD than barium radiography.<sup>45</sup> It will show an ulcer in the stomach or proximal duodenum, confirm perforation and enable histology and biopsy for H. pylori test and cancer. However, tests may give false-negative results in patients taking proton-pump inhibitors, bismuth, or other medications. Switching to an H2RA for 2 weeks prior to endoscopy is an alternative, especially in patients without red-flag features. In the absence of red flags or failure of patient to respond, endoscopy is often unnecessary in primary care and is only indicated if symptoms persist. However, in patients with red-flags or who are > 50 years of age, have family history of gastric carcinoma or previous stomach surgery, an endoscopy should be ordered immediately.<sup>24,46</sup>

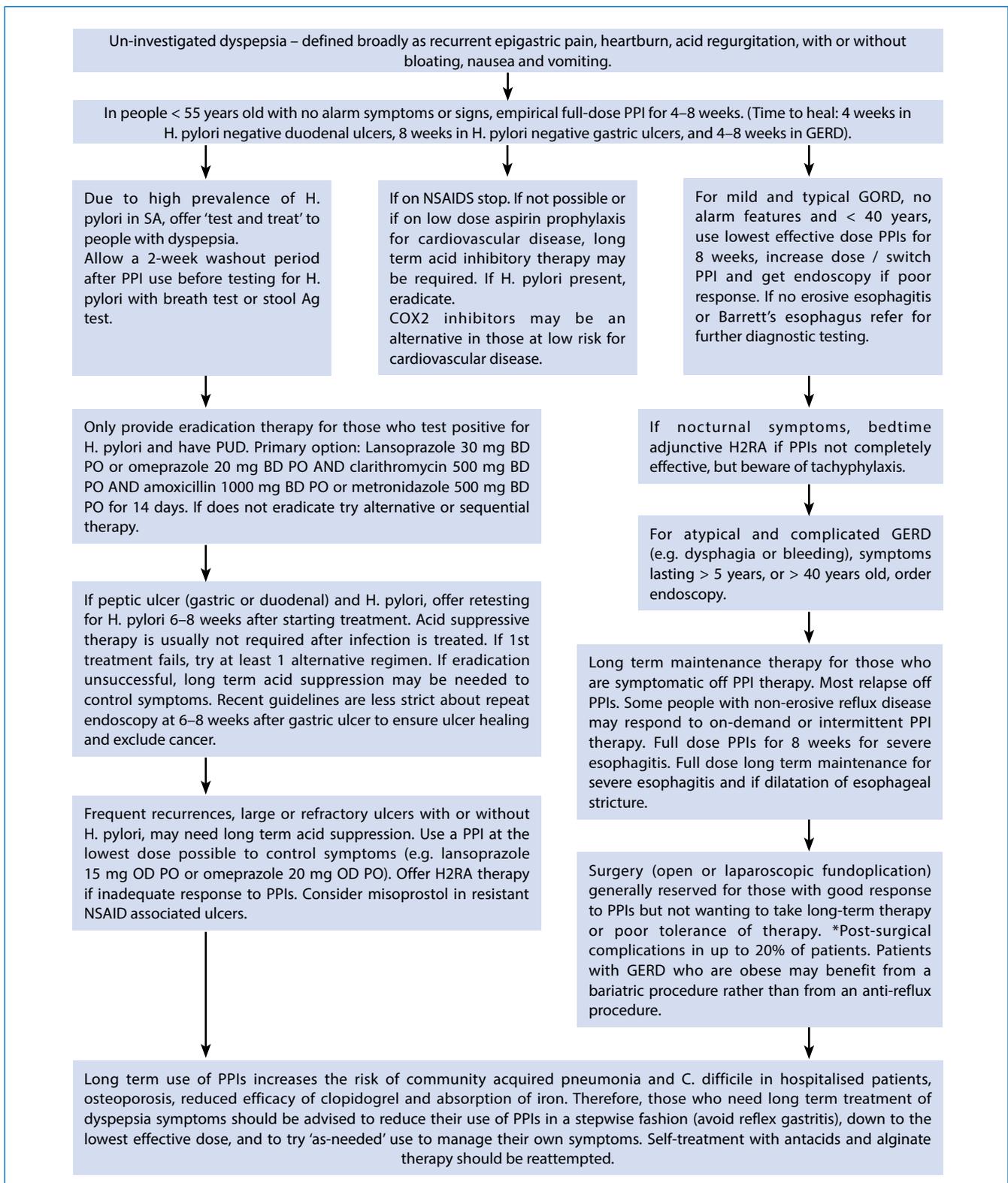
**2. A positive test for H. pylori:** South Africa has high prevalence of H. pylori infection (> 10–15%) and in the absence of red-flags, the test and treat approach is recommended.<sup>42,43</sup> Validated, non-invasive tests such as breath and stool antigen tests are more accurate than antibody tests and are recommended. If tests are not easily available in a high prevalence area, H. pylori infection should be assumed, and empiric eradication treatment given. False positive results are high in low prevalence populations and routine H. pylori testing is not recommended, except when the patient fails to respond to empiric treatment or relapses rapidly on stopping acid suppression treatment.

**3. Other investigations<sup>45</sup>:**

- Stool haem test for occult blood
- Full blood count in the case of anemia or bleeding
- Fasting serum gastrin level, if Zollinger Ellison syndrome is suspected [multiple or refractory ulcers, distal to duodenum, diarrhoea or a family history of multiple endocrine neoplasia (MEN1)]
- Plain erect abdominal radiograph or barium contrast studies may show air under the diaphragm

**Table 4:** Risk factors associated with PUD<sup>43,45</sup>

Strong associations	Weak associations
H. pylori infection (Africa has highest incidence in the world. More common in duodenal ulcers causing gastrin and acid hypersecretion, than gastric ulcers causing local mucosal damage. Eradication leads to reduced recurrence of ulcers and bleeding.)	ABO blood group (Associations shown in older studies before H. pylori was known.)
NSAID use (More commonly cause gastric ulcers. Relief with antacids may support diagnosis, but not sensitive or specific. Increased risk associated with age > 60, previous history PUD, dose and duration, concurrent H. pylori or corticosteroid use. Low dose aspirin may increase risk.	Alcohol (lack of good evidence)
Smoking (associated with 23% of all ulcers) Incidence and complications increase with age.	Psychological stress (lack of good evidence)
Previous history/family history of PUD (related to persistent H pylori infection)	
Admission to Intensive Care Unit (stress ulcers)	

Figure 1: Algorithm for the management of dyspepsia in primary care<sup>8,39,45,52</sup>

## Differential diagnosis

Table 5 lists differential diagnoses that need to be considered, especially cardiac and biliary diseases.

## Management

Management approaches are summarised in Figure 1. The goals of therapy are to relieve symptoms, heal ulcers, eliminate the underlying cause if possible and treat complications.

**1. H. pylori eradication<sup>42,47,48</sup>:** Generally, leads to ulcer healing with less than 20% of patient experiencing recurrence. Success of treatment is mainly limited by antibiotic resistance and patient adherence. Fourteen days of triple therapy (a PPI plus 2 antibiotics) is recommended as this duration significantly increases H. pylori eradication. However, 7 days of quadruple therapy (PPI plus bismuth plus 2 antibiotics) and 10 days of sequential therapy (i.e., 5 days of a PPI plus amoxicillin,

followed by 5 days of a PPI plus clarithromycin and tinidazole) may address the problem of antibiotic resistance and provide improved eradication rates. There are no trials that have confirmed the superiority of the modified sequential therapy over standard triple therapy.<sup>49</sup>

In populations with low prevalence, *H. pylori* eradication may be omitted and an empiric trial of acid suppression with a PPI for 4–8 weeks is an acceptable initial management. In patients that respond, treatment is stopped after 4–8 weeks, and if symptoms reoccur, another course of treatment is justified. However, if initial acid suppression fails after 2–4 weeks, the class of medications or dosing should be changed, *H. pylori* tested and treated before sending for endoscopy.

**2. Acid suppression:** Many drug classes of gastroprotectants are effective.<sup>50</sup> PPIs have simple dosing regimen, inhibit gastric acid secretion to a greater extent and heal peptic ulcers more rapidly than Histamine 2 receptor antagonists (H2RA). They are the drug of choice.<sup>9,51</sup> However, H2RA may be used if the patient is unresponsive to PPIs. Sucralfate has similar ulcer healing rates to H2RA and coats the ulcer base, promoting ulcer healing. Frequent dosing and large tablet size results in poor adherence. Antacids are relatively ineffective and slow to

produce ulcer healing, but misoprostol may be used in NSAID-induced ulcers refractory to PPI.<sup>45</sup>

**3. Lifestyle modification:** Recommendations include smoking cessation, limiting alcohol, small frequent meals and stopping NSAIDs.<sup>46</sup>

**4. Referral for surgery:** May be indicated for patients with chronic ulcer unresponsive to 2nd line drug treatment, intestinal perforation, upper gastrointestinal bleeding and outlet obstruction. The last three are life threatening and require immediate resuscitation and referral to a gastroenterology unit.

## Conclusion

GERD and PUD impose significant negative effects on the quality of life of patients with these diseases. While empiric treatment with PPIs suffices for most patients with GERD, patients with PUD in developing countries, including South Africa, need *H. pylori* eradication treatment and acid suppression therapy. Endoscopy is not routinely done in primary care for GERD and PUD but patients with poor response or recurrence after treatment, those who present with complications or red-flags, Barrett's esophagus and those who meet other criteria for endoscopy, should be referred for one.

**Table 5:** Key messages

- Co-existing heartburn and regurgitation have high diagnostic accuracy for GERD. Response to an empiric treatment with PPI is confirmatory.
- Endoscopy should not be routinely done for uncomplicated GERD. However, patients with Barrett's esophagus and those with complications of GERD need endoscopy.
- Lifestyle modification and acid suppression with PPI are cornerstone of GERD management.
- Surgical interventions are only indicated in patients with complications and those unresponsive to management.
- In primary care, endoscopy is not routinely performed for uncomplicated PUD. However, patients aged > 50 years, those with recurrence, complications, gastric ulcer, family history of gastric cancer, history of gastric surgery and red-flag symptoms should have endoscopy.
- Empiric eradication of *H. pylori* infection and acid suppression with PPIs are the key strategies in the management of uncomplicated PUD.
- In high prevalence settings such as South Africa, test (using non-invasive tests) and treat approach should be employed for *H. pylori* eradication. If resources are limited, *H. pylori* infection should be assumed to be present and empiric triple therapy treatment given.
- Routine testing and eradication of *H. pylori* is not recommended in low prevalence settings.

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