Austin Journal of Gastroenterology

Open Access

Austin Publishing Group

Special Article - Peptic Ulcer Disease

# Peptic Ulcer Disease

**Lauret ME, Rodriguez-Peláez M, Pérez I and Rodrigo L***

Central University Hospital of Asturias (HUCA), Oviedo, Principality of Asturias, Spain

***Corresponding author:** Luis Rodrigo, Gastroenterology Service, Central University Hospital of Asturias (HUCA), Oviedo, Principality of Asturias, Spain

**Received:** October 29, 2015; **Accepted:** November 17, 2015; **Published:** November 19, 2015

**Abstract**

Peptic Ulcer Disease (PUD) it is a very prevalent condition, because it affects around 5-10% of the general population worldwide, but with no table regional and racial variations. The two most common etiological causes are the chronic infection with Helicobacter Pylori (Hp) and the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Its diagnosis is based mainly in the endoscopy and the active search of concomitant Hp presence. The discovery of the link between *H. pylori* and peptic ulcer has changed dramatically its management, because it has become a curable infectious disease.

The eradication treatment of Hp (+) is the best choice for achieve the final cure of the PUD in infected patients. Several current international guidelines recommend a standard triple therapy as first-line therapy, including a proton pump inhibitor and a combination of amoxicillin and clarithromycin. This combination therapy has shown a decreasing efficacy over the years. The main reason is the increasing antibiotic resistance, particularly to clarithromycin and metronidazol, of certain Hp strains. Several new treatment options or modifications of already established regimens have been introduced in last year's, to overcome these treatment failures.

For the subgroup of patients with H. pylori-negative ulcers, NSAIDs stop intake also has a clear influence in the evolution of the disease and in some cases drives to the complete healing of the peptic ulcer. In refractory or recurrent cases, continuous therapy with anti-secretory agents and/or the replacement of conventional NSAIDs by selective drugs for inhibition of Cyclooxygenase-2 (COX-2) are useful treatment options.

**Keywords:** Peptic ulcer disease; Helicobacter pylori; Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); Eradication treatment

## Definition and Etiology

Peptic Ulcer (PU) can be defined as the presence of apro found loss of substance affecting the mucosa of the stomach and/or duodenum, reaching beyond the muscular is mucosa generally to the muscle layer remain active due to the presence of environmental gastric acid secretion.

The two most common etiological causes are the chronic infection with Helicobacter pylori (Hp) and the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), including of course, the Acetyl Salicylic Acid (ASA).

There are other less common causes also that can cause PU, which considered together, account for less than 5% of cases. Among them is the Zollinger-Ellison syndrome or gastrinoma, because it is a neuroendocrine tumor, usually located at the head of the pancreas or in the duodenal wall, over active and gastric secretory (Table 1).

However, we must remember that approximately 5-15% of patients considered Hp negative, despite performing wide comprehensive etiological studies, do not get to find again the precise cause of PU, which are referred to as "idiopathic".

Tobacco abuse and O blood group are considered to be both risk factors for the development of ulcer disease. Regarding the existence of genetic factors is unknown, although some cases with familial aggregation can occur. Tobacco consumption, difficult ulcer healing and promote sits recurrences, especially in patients Hp (+) or in common NSAIDs takers.

There are certain, both digestive and extra-digestive diseases, most frequently associated with peptic ulcer, among which are included the concomitant presence of chronic Gastro Esophageal Reflux Disease(GERD), Barrett's esophagus, Chronic Obstructive Pulmonary Disease (COPD), liver cirrhosis, chronic renal failure, while in other clinical situations, their presence is lower, as in the atrophic gastritis, Addison's disease, autoimmune thyroiditis and hyperparathyroidism.

## Epidemiology

It's a fairly hetero generous disease worldwide distribution, but the disease affects to people from all countries and different races. Its average prevalence is between 5-10% of the general population over a lifetime.

This represents approximately around the10-20% of people infected with Helicobacter pylori globally, with wide variations between different races and countries of the world having been confirmed, as its prevalence is inversely related to the economic level of the population, degree of development and level of hygienic social environmental. The average incidence of peptic ulcer among the persons infected by Hp is approximately1% per year [1-4].

The prevalence is alike for both sexes. The adjusted incidence in




**Citation:** Lauret ME, Rodriguez-Peláez M, Pérez I and Rodrigo L. Peptic Ulcer Disease. Austin J Gastroenterol. 2015; 2(5): 1055.

**Table 1:** Etiology of PUD.

| Common causes | Infrequent causes |
|---|---|
| - Helicobacter pylori<br>- NSAIDs and ASA<br>- Stress ulcers | - Gastrinoma (Zollinger-Ellison syndrome)<br>- Hyperplasia/hyper function of antral G cells<br>- Systemic mastocytosis<br>- Myeloproliferative Syndromes with basophilia<br>- Viral infections (herpes simplex virus tipo I and cytomegalovirus)<br>- Vascular insufficiency (cocaine)<br>- Radiation<br>- Chemoembolization (via hepatic artery)<br>- Crohn´s Disease<br>- Type II amyloidosis<br>- Neuhauser syndrome (tremor-nystagmus-ulcer)<br>- Porphyria cutanea tarda<br>- Other drugs (potassium chloride, bisphosphonates, and mycophenolate)<br>- Idiopathic |

relation to age, some expats establishes regarding the average age of onset gastric and duodenal ulcer Between, So that the peak incidence of the gastric ulcer is between 55-65 years, while the average age of duodenal ulcer onset is a decade earlier, at around 45 years.

There are significant epidemiological differences worldwide. So, in developing countries the prevalence of Helicobacter pylori infection is much higher (2-5 times) than in developed, probably because of the worst existing hygiene and dietary conditions that favor the transmission of infection. There are also clear differences as regards the use of antibiotics and NSAIDs. This also justifies that the percentage of negative Hp peptic ulcers is much less in developing, compared with the observed percentages found in developed countries [5-7].

## Pathogeny

The mechanisms, through which the Hp favors the development of PU, are better known in the duodenal, than in gastric side. In patients infected, the bacteria trigger an inflammatory and immunological response to the level of the gastric and duodenal mucosa, with release of a number of pro-inflammatory cytokines such as IL-8and TNF-α. Thus appears acute and chronic gastritis, which reduces the thickness and quality of mucus layer.

In Hp infected patients, gastric hyper secretion occurs, due to a decrease in the density of the antral D cells and therefore decreased secretion of somatostatin, which determines a loss of inhibitory stimulus. The resulting hyper gastrinemia stimulates gastric parietal cells, causing an increase of acid secretion, with decrease of pH in the lumen of the stomach and duodenum, which also continuously determines the appearance of duodenal gastric metaplasia level. This in turn, causes the duodenal mucosa impair its ability to segregate bicarbonate, thus facilitating duodenitis development and later onset of duodenal ulcer. After Hp eradication, the gastrin levels return to normal [8,9].

Ulcerogenic potential of different Hp strains vary in terms of their ability to produce among others, the Cytotoxic Protein (CagA) and the so-called Vacuolating Protein (VacA) [10].

Consumption of NSAIDs and/or ASA is the second most common cause of ulcers. Both groups of drugs, are causative agents in 70-85%, once safely ruled out the presence of Hp. Overall, it is estimated that they may cause up to 10% of duodenal ulcers and 20-30% of gastric. It is estimated that up to 50% of chronic NSAID takers have little clinically relevant erosive lesions, ulcers may reach up to 30%, of which about 1% annually, are complicated [11].

The mechanisms, by which NSAIDs cause damage to the gastric and duodenal mucosa, are mainly two. On one hand, these drugs behave as weak non-ionized acids, that can penetrate into the mucus layer easily, and inside the epithelial cells. Another and most important effect is the ability of cyclo-oxygenase inhibitory enzyme, thereby decreasing the intracellular concentration of prostaglandins. These play an important role in maintaining the integrity of the gastro duodenal mucosa role, because of its intra mucosal vasodilator effect maintaining intact the blood flow and secondarily stimulate the local secretion of mucus and bicarbonate, facilitating the cell turnover and epithelization [12,13].

## Clinical Manifestations

The most typical manifestation of the uncomplicated peptic ulcer is the presence of a burning or corrosive pain, mainly located at the epigastrium. Sometimes, it can be characterized as a vague abdominal pain, nausea, vomiting, diffuse discomfort, or may be perceived as a pressure or feeling of abdominal fullness or hunger.

Typically, it appears during the fasting state, between 1 and 3 hours after eating or at night. It can also occur in relation to stress situations.

This epigastric pain typically is relieved by eating any kind of food or taking antacids pills in few minutes, and reappears cyclic ally again, within about 2 hours. Symptoms may persist for several days, weeks or months. Two thirds of patients with duodenal ulcer refer that the pain wakes the mat night, being uncommon to have pain upon waking in the morning. There is infrequent that these patients present anorexia and/or weight loss. By contrary, most of them often manifest hyperphagia and weight gain, probably because the pain usually subsides with ingestion of food. This is the well known three steps sequence of "pain/ingestion of food/alleviation"

Sometimes the pain radiates to the back or right upper quadrant suggesting that the appearance of an ulcer of the probable localization at the posterior surface of the duodenal bulb, even if it lose the characteristic rate of three steps and becomes continuous and intense. Then, it can be considered to have a penetrating complication to the pancreas.

In the gastric ulcer, the pain usually also occurs in the postprandial period, and appears earlier than in the duodenal ulcer and does not alleviate with the food intake and/or antacids. Only a third of the patients wake up at night by pain, and up to 50% may have anorexia and weight loss, because of a concomitant delayed gastric emptying [14].

The classic clinical pattern in three steps has low sensitivity, appearing only in 50-70% of duodenal ulcers and in less than 50% of gastric ulcers. It is also less specific, since patients with dyspepsia and GERD may also have shown very similar symptoms. On clinical examination, the most common finding is to find pain on palpation at the epigastrium.

However, in many patients, ulcers can be asymptomatic and the first manifestation may be related to the presence of one ulcer-related complication, especially in elderly patients who take NSAIDs. It has been proposed that NSAIDs may mask pain of ulcer processes [15].

Possible differential diagnoses should include multiple entities such as functional dyspepsia, gastro esophageal reflux disease, gastric cancer, gallbladder or pancreatic disease. When symptoms are in concordance with the presence of a peptic ulcer, objective evidence is needed to confirm the diagnosis.

After the symptoms improvement, is frequently observed to have recurrences. The most important factors explaining ulcer recurrence are concomitant Helicobacter pylori infection not eradicated and frequent use of NSAIDs. Eradication of Helicobacter pylori has dramatically changed the natural history of the PUD, preventing their recurrences. Moreover, NSAIDs stop intake also has a clear influence in the evolution of the disease and in some cases drives to the complete healing of the peptic ulcer.

## Complications

Several complications can occur in patients with peptic ulcer disease of any etiology. They are the main reasons for the high morbidity and mortality associated with this disease found until now.

The routine application of different gastro protection strategies and eradication therapies for Helicobacter pylori infection, have reduced significantly the incidence relative to that seen in the previous decades. They are more common in habitual smokers and chronic NSAIDs users [16,17]. There are four major complications of peptic ulcer disease: Bleeding, perforation, penetration and obstruction.

## Bleeding

Although its incidence has declined a little in the recent years; however remains being the most common complication and appears in around10-20% of patients. It is a frequent cause of admission in emergencies.

Ulcers NSAIDs related are more likely to bleed than those caused only by Helicobacter pylori chronic infection. Populations at a greatest risk are the elderly and those with other serious conditions, such as respiratory, cardiac, cerebrovascular o renal problems.

A total of 80-90% of upper gastrointestinal hemorrhage are from not variceal bleeding origin, and around 40-50% of these are caused by peptic ulcer disease. The mean associated mortality is around, 5%

It can take various clinical manifestations: 15% have melenas, 30% hematemesis, 50% have both and about 5% has hematochezia caused by severe bleeding.

In other cases, ulcer bleeding may have a chronic course, manifestating as iron deficiency anemia or a positive fecal occult blood. There is a strong correlation between ulcer bleeding and use of NSAIDs or aspirin, because these drugs predispose to ulceration and inhibition of platelet aggregation [18].

Although not seems that the exclusive use of corticosteroids substantially increase the risk of ulcer bleeding, the combined use of these drugs together with NSAIDs, may increase by tenfold the risk of this complication [19,20].

## Perforation

It occurs in up to 5% of patients with peptic ulcer. Usually correspond to 60% of duodenal ulcers cases, most of them located at the anterior wall of the duodenal bulb and 40% of gastric ulcers, often affecting lesser curvature. Free perforation of a duodenal or gastric ulcer into the peritoneal cavity may endanger the patient's life.

It usually appears as a sudden, severe abdominal pain, located in the epigastrium, which may radiate to back or become diffuse and associated with acute shock suggests a complicated ulcer perforation with peritonitis.

Typically the patient usually remains motion less, his thighs flexed on the abdomen giving the impression of gravity. On examination, a hard, rigid abdomen is seen wither bound. Auscultation may initially show increased intestinal noises and as the condition progresses, they diminish and finally almost disappear. Around 70% of cases, present visible pneumoperitoneum at plain radiologic abdomen.

The etiology of duodenal ulcer perforated appears to be multi factorial such as alcohol, tobacco, Helicobacter pylori, and especially intake of NSAIDs, since more than a third of the perforations are related to taking these, even to reaching figures of up to 50%, mainly in the elderly and being sometimes the only acetyl salicylic acid NSAID used even in small doses [21,22]. Another cause although much less common, is cocaine chronic consumption. The patho physiology of duodenal ulcer perforated by cocaine remains speculative. Chances are that perforation occurs by a localized vasoconstriction or vascular thrombosis [23]. It has been reported that in these cases the majority (40%) are placed mostly in juxta-pyloric area.

## Penetration

This complication occurs when an ulcer cross the wall of the stomach or duodenum, but instead of drilled freely into the peritoneal cavity, burrow into an adjacent organ. It occurs in approximately 25% of duodenal ulcers and 15% of gastric ulcers. Adjacent organs that extend most often are the pancreas, liver or omentum.

The clinical presentation may be similar to that of uncomplicated ulcer but the pain is usually more severe and persistent [24]. Pain cannot be relieved by eating, or even may worse and more often, wakes the patient at night. Typically, pain radiating to the back, when an ulcer penetrated to the pancreas or to right upper quadrant, appears when penetration is in the gastro hepatic omentum.

Rarely, penetrating peptic ulcers may form fistulas between the duodenum and bile duct (choledoco-duodenal fistula) or between the stomach and colon (gastro-colic fistula).

## Obstruction

It is an uncommon complication, which represents approximately 5% of ulcer-related complications. Until about 1970, peptic ulcers represented the most common cause of obstruction to gastric emptying [25]. In the last years, however, has decreased the frequency of obstruction secondary to peptic ulcer and currently gastric malignancies are the leading cause of gastric outlet obstruction [26].

Ulcers that cause obstruction are usually located in the pyloric channel or duodenal bulb, usually occurring as a result of the swelling

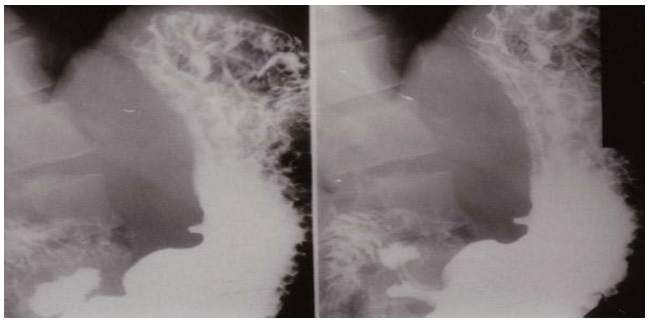

**Figure 1:** A benign gastric ulcer at the lesser curve.

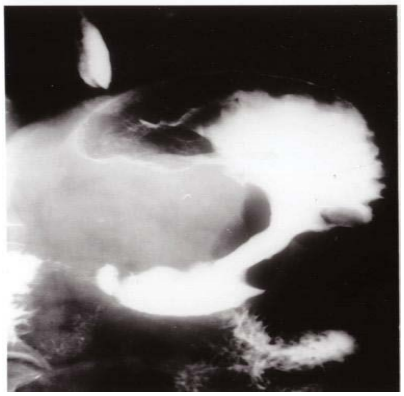

**Figure 2:** Malignant lesion in the gastric body.

and edema accompanying active ulceration or the healing process of the ulcer and shrinkage.

The main symptoms of obstruction are nausea, vomiting, early satiety, and anorexia. Vomiting tends to occur between 30and 60 minutes after meals an patients are often satisfied for hours after meals.

On clinical examination, they may show signs of thinning and dehydration and splash produced by air and liquid retained within the intended stomach.

The diagnostic suspicion should be confirmed by endoscopy that also will serve to exclude a possible malignant origin stenosis.

## Diagnosis

It is mandatory to perform a good clinical history and a complete physical examination, in order to make a complete data collection of all the symptoms and signs of PUD. Also, it is extremely important to register all the past medical antecedents, and the duration of alcohol intake, history of NSAIDs and smoking consumption, and also for the possible existence of previous episodes of peptic ulcer.

There are two major considerations in the diagnosis of peptic ulcer. One is to assess if the referred symptoms are or not related to functional dyspepsia and the second is to determine the specific etiology of the ulcer.

## Radiology

Barium gastro duodenal studies have been almost completely relegated and happily substituted by the endoscopic explorations in the routine diagnostic protocols, although they can still be useful in few patients who refuse to perform it, or in the cases that endoscopy is inaccessible by narrowing of the esophagus. The sensitivity and specificity of barium radiographic studies, depends on the radiologist experience, the technique used, the size of the lesion (if they are <0, 5 cm in diameter, it can be difficult to detect) and ulcer depth. Radiologic signs suggesting on benign nature are regular margins and symmetrical mucosal folds, a smooth translucent band or collar, surrounding the ulcer crater suggesting edema and indentation of the opposite wall (Figure 1). The signs that suggest malignancy by contrary are a big size of the ulcer, irregular mucosal folds, contrast absence or irregular filling (Figure 2).

## Endoscopic Findings

Upper GI endoscopy is the most accurate diagnostic test for PUD. It gives information about the size and the location of the lesion. In addition, mucosal biopsies can be performed, in order to do a differential diagnosis and to carry out endoscopic treatments in case of bleeding peptic ulcer.

The signs suggesting benign origin are the presence of regular mucosal folds surrounding the ulcer base and the fibrin deposit at the crater base (Figure 3). The feature that suggests malignancy, are the finding of overhanging margins, irregular or thickened borders and/or the presence of an ulcerated mass, that protrudes into the lumen (Figure 4).

Malignancy of the duodenal ulcers is exceptional. Therefore, it is rutinary biopsy is not recommended. However, it is mandatory

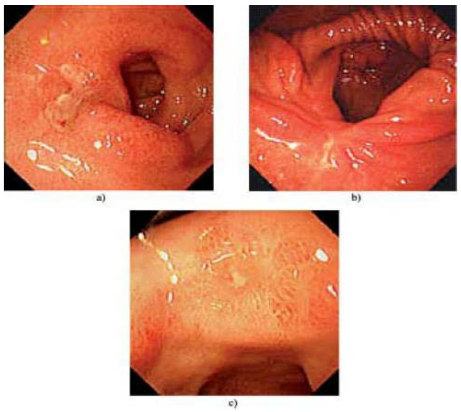

**Figure 3:** Endoscopic images a) Active ulcer. b) Ulcer scar c) Last stage of the mucosal healing, in benign peptic gastric ulcers.

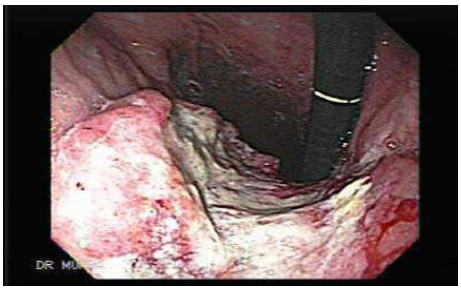

**Figure 4:** Endoscopic picture of malignant gastric fundus ulcerated lesion (view by retroflexion).

**Table 2:** Diagnostic methods for Helicobacter pylori infection.

| | Sensitivity (%) | Specificity (%) |
|---|---|---|
| **A.- Direct methods** | | |
| Rapid urease test | 85-95 | 95-100 |
| Histology | 85-95 | 95-100 |
| Gram | 90 | 90-100 |
| Culture | 75-90 | 100 |
| **B.- Indirect methods** | | |
| Serology | 85-95 | 80-95 |
| Urea breath test | 90-100 | >95 |
| Stool antigen test | 90-100 | 90-100 |

**Table 3:** Selection of diagnostic method for the Hp infection in different situations.

| |
|---|
| **1.-While performing an endoscopy in which we find a duodenal or gastric ulcer** |
| •Rapid urease test + histology |
| **2.- Medical history of peptic ulcer (gastric or duodenal), asymptomatic patient** |
| •Urea breath test ($^{13}$C-UBT) |
| •Validated serology |
| **3.- While performing an endoscopy for gastrointestinal bleeding due to peptic ulcer** |
| •If not active bleeding is detected: Rapid urease test + histology |
| •If active bleeding is detected or the rapid urease testing was negative: Urea breath test ($^{13}$C-UBT) |

to take several mucosal biopsies form the margins at any gastric ulcer, despite it is benign appearance. A follow-up endoscopy will be performed until the healing is completed [27].

The presence of Helicobacter pylori infection must be investigated in every patient presenting peptic ulcer. Since it is discovery in 1983, the management has changed a lot. It is known that the prevalence of the infection increases with the age, and there is no difference between women and men.

Diagnostic tests for helicobacter pylori are divided into direct (based upon the need for endoscopy) and indirect tests, and several are used not only for diagnosis, but also in the follow-up after the eradication treatment in order to confirm this one (Tables 2 and 3) [28].

## Treatment

The discovery of the link between *H. pylori* and peptic ulcers has changed dramatically its management, because it has become a curable infectious disease. For the subgroup of patients with *H. pylori*-negative ulcers, the therapy with anti-secretory agents or the replacement of conventional NSAIDs by selective drugs for inhibition of Cyclooxygenase-2 (COX-2) are other treatment options.

## General Care

It is essential to avoid potential contributing agents such as NSAIDs or tobacco. There are no firm recommendations on alcohol intake or dietary habits, apart from not eating foods that can aggravate the symptoms [29].

## Helicobacter Pylori-negative

The main etiology is related to the use of NSAIDs, so withdrawing these treatments is a crucial step. In H. pylori-negative, NSAID-negative ulcers, a detailed search should be made to detect other contributing factors, such as medical co morbidities, poor nutritional status, and ischemia and acid hyper-secretary disorders. The management of uninfected patients is based on the classic anti-secretory therapy [29,30].

The two groups of anti-secretory drugs most commonly used in these conditions are the Histamine-2 Receptor Antagonists (H2RAs) and the Proton Pump Inhibitors (PPIs). The mechanism of action is by suppression of acid secretion by gastric parietal cells. First drugs got the effect by blocking the histamine H2 receptors placed on the cell basolateral membrane and the latter by irreversible binding and inhibition of the hydrogen-potassium ATPase pump, located on the luminal surface of the cell membrane. All PPIs achieve a similar level of acid secretory inhibition and healing rates in the treatment of PUD.

The recommended schedule for each of these drugs is the standard dose once a day during four and 6-8 weeks, for acute duodenal and gastric ulcers respectively. H2RAs are well absorbed after oral dosing and is not reduced by concomitant food intake. PPIs are most effective when taken 30-60 minutes before meals. Global ulcer healing rates are above 75%, although PPIs achieve better results than H2RAs (near 100%). Therefore, the use of PPIs is recommended whenever possible. If a standard PPI therapy fails to heal a peptic ulcer, it is recommended to try twice daily dosing or switch to another PPI. For large ulcers (>2-3 cm), double dose of PPI is recommended for 12 weeks. Higher doses are necessary to control symptoms in other hyper secretory states, such as the Zollinger-Ellison syndrome.

The probability of ulcer recurrence with the classic anti secretory therapy is approximately 80% per year, after the end of treatment. For this reason, a long-term maintenance treatment with a PPI is recommended in patients with increased risk, defined by a history of previous complications, frequent recurrences, torpid evolution (refractory, giant or fibrosed ulcers) or when NSAIDs cannot be discontinued. For this latter condition, the use of COX-2 inhibitors as an alternative requires a careful individual assessment of the possible gastrointestinal and cardiovascular risks. There are no conclusive data from controlled trials, regarding the appropriate duration of prolonged therapy, although this should be maintained at least until ulcer´s healing has been confirmed, or NSAIDs have been stopped.

The H2RAs and PPIs are usually well tolerated with a low incidence (<3-4%) of side- effects [29,31]. Most are reversible and mostly occur in patients over 50 years old. For H2RAs, it is advised to perform some dose adjustments in patients with renal failure. Ranitidine binds to Cytochrome P-450 (CYP) enzyme system and may inhibit the elimination of other drugs that are metabolized through the same metabolic route.

PPIs are remarkable safe drugs and do not require dose adjustments for renal or liver insufficiency. The main concerns regarding the long-term use of these agents include the presence of hypergastrinemia produced by the inhibition of acid secretion and the association with gastric atrophy. However, so far, it has not been yet reported any significant clinical consequences of these risks. Other adverse effects of prolonged PPIs use, such as potential onset of enteric infections (*Clostridium difficile*) and nutritional deficiencies (hypomagnesaemia, decreased calcium absorption with increased

**Table 4:** Recommendations for pharmacological treatment of PUD.

| | | | |
|---|---|---|---|
| **1.- Helicobacter pylori-negative peptic ulcer disease** | | | |
| **Histamine-2 receptor antagonists (H2RAs)** :<br>Ranitidine: 300 mg, Famotidine: 40 mg, Cimetidine: 800 mg<br>**Proton pump inhibitors (PPIs)** :<br>Omeprazole: 20 mg, Esomeprazole: 20 mg, Lansoprazole: 30 mg,<br>Pantoprazole: 40 mg, Rabeprazole: 20 mg | | | |
| **2.- Helicobacter pylori-positive peptic ulcer disease** | | | |
| *Triple therapy* | PP<br>Amoxicillin<br>Clarithromycin | Double dose*/12 h<br>1 gr/12 h<br>500 mg/12 h | 10-14 days |
| *Triple therapy*<br>*(Penicillin allergy)* | PPI<br>Metronidazole<br>Clarithromycin | Double dose*/12 h<br>500 mg/12 h<br>500 mg/12 h | 10-14 days |
| *Quadruple therapy*<br>*(Concomitant Therapy)* | PPI<br>Amoxicillin<br>Clarithromycin<br>Metronidazole | Standard dose/12 h<br>500 mg/12 h<br>500 mg/12 h | 10-14 days |
| *Rescue treatment (After failure of triple or concomitant therapies)* | PPI<br>Amoxicillin**<br>Levofloxacin | Standard dose/12 h<br>1 gr/12 h<br>500 mg/12-24 h | 10 days |
| *Rescue treatment (After failure of triple or concomitant therapies)* | PPI<br>Bismuth<br>Tetracycline<br>Metronidazole | Standard dose/12 h<br>120 mg/6 h<br>500 mg/6 h<br>500 mg/8 h | 10-14 days |

*Omeprazole 40mg, Lansoprazole 60mg, Pantoprazole 80mg, Rabeprazole 40mg, Esomeprazole 40 mg.
**In patients with penicillin allergy, a Levofloxacin-containing regimen (together with a PPI and clarithromycin) represents a second-line alternative.

risk of bone fractures, vitamin $B_{12}$ deficiency) should be considered. PPIs are metabolized by cytochrome P450 enzymes, with CYP2C19 having the main role, and the dominance of this route varies among the different agents, which can lead to changes in the interaction profiles. In this regard, it has been described that pantoprazole has the lowest potential for P450 metabolism and drug interactions [32]. The antagonism between PPIs and clopidogrel has been one of the most relevant described. However, the potential clinical negative impact of some PPIs on the therapeutic effect of clopidogrel remains controversial. In view of the inconclusive data, PPIs with weaker inhibition power of CYP2C19 are preferred in combination with clopidogrel, compared with those with stronger inhibition such as omeprazole [33].

## Helicobacter Pylori-Positive PUD

The eradication therapies of *H. pylori* infection are based on the scientific evidence, collected in the most recent consensus reports [34]. In settings with a high prevalence of *H. pylori* infection and in the absence of NSAID use, is reasonable to consider the empiric eradication treatment. Drugs that have demonstrated efficacy include amoxicillin, clarithromycin, metronidazol, tetracycline and bismuth (Table 4).

The most recent data show that classic triple therapy containing PPI clarithromycin and amoxicillin or metronidazol has lost some efficacy, mainly due to the increase resistance to clarithromycin observed in the latest years. For this reason, this standard regimen is currently recommended for first-line treatment, only in areas of low resistance rate. Double doses of PPI (twice daily) and extend treatment to 14 days improve the eradication rates. In regions with high clarithromycin resistance, quadruple therapy (the so called "concomitant" treatment) which includes the combination of PPIs, amoxicillin, clarithromycin and metronidazol, is recommended as first-line empirical treatment. If these combinations fail to achieve the eradication, either a bismuth-containing quadruple therapy, or a rescue treatment with levofloxacin, are recommended. After the failure with three different regimens, it is better to refer the patient to a center with greater expertise in the management of multi-drug resistant *H. Pylori*.

*H. pylori* eradication alone should be considered sufficient for small or moderate size ulcers and for compliant patients with confirmed eradication, in the absence of NSAIDs use. Patients with gastric ulcers, complicated duodenal ulcers or other markers of increased risk (giant ulcers, fibrosed lesions or prior history of relapse) require maintenance treatment with anti secretory drugs, at least until the eradication of *H. pylori* and/or ulcer healing, have been confirmed. Long-term therapy with normal dose of PPIs is indicated in these high-risk subgroups, if the infection persists.

The combined treatments are generally well tolerated and the rates of adverse effects depend on the antibiotics used in the different treatment regimens. The most frequently registered are diarrhea, rash and candidiasis (amoxicillin); nausea, metallic taste, peripheral neuropathy and anta bus-like effect with alcohol intake (metronidazol); prolongation of QT interval and seizures can appears in predisposed patients for other reasons (fluoroquinolones) and in few cases transient pigmentation of the tongue and dark stools (bismuth).

## Endoscopic Surveillance

An endoscopic control is recommended to monitor the healing in giant duodenal ulcers and gastric ulcers, regardless of their size. In this last case, repeat the procedure with biopsy after 6-8 weeks of treatment, is a good way to ensure that the lesions are benign.

## Treatment in Special Situations

### *H. pylori* infection in NSAIDs users

*H. Pylori* infection is associated with an increased risk of the development of gastro duodenal ulcers and its complications in

NSAIDs and low-dose aspirin users [34]. The available data support *H. pylori* eradication before starting NSAIDs treatment. It is also appropriate to test and treat this infection, following the presentation of any clinical ulcer. If NSAIDs or aspirin are continued, treatment of such patients with a PPI in addition to the eradication therapy can reduce the risk of recurrent ulcer complications.

### Refractory ulcers

Peptic ulcers that have not healed after proper treatment for 12 weeks are considered refractory lesions [29]. In this context, the following conditions must be investigated: Persistence of *H. pylori* infection or false negative in the initial diagnosis, hidden NSAIDs use, non-compliance of prescribed treatment, giant or fibrotic ulcers, ulcerated tumors, tobacco consumption and acid hyper secretory states. In the absence of these risk factors, it is recommended to insist on all medical options before indicating surgery.

### Pregnancy and lactation

Omeprazole is listed by the FDA as a pregnancy class C medication, whereas all other currently available PPIs, and H2RAs such as cimetidine and ranitidine, are class B. Although the results in some analysis of prospective data have shown that the global risk is low in pregnancy with potential toxicity during lactation, the lack of data in humans precludes achieving definitive conclusions regarding their safety [35].

Currently, there are no guidelines to treat *H. pylori* infection during pregnancy. It has been suggested that eradication should be deferred after delivery and lactation [36].

### Stress-related erosive syndrome

These lesions are typically described affecting to patients admitted in intensive care units and affected with a serious systemic disease, such as sepsis, major trauma, massive burn injury and multiorgan failure. In this scenario, coagulopathy and mechanical ventilation have been identified as the most important risk factors for stress-related complications [29,30]. The approach to treatment of these lesions is similar to that for the rest of peptic ulcers. Routine prophylaxis is only recommended in patients at high-risk of stress ulcer bleeding. It has been suggested that PPIs are more effective than H2RAs in preventing clinically important and overt upper gastrointestinal bleeding [37].

## Treatment of Complicated PUD

### General approach

All patients with complicated peptic ulcer disease require appropriate supportive care, such as fluid resuscitation, administration of acid suppressive therapy, *H. pylori* infection treatment, if present, and discontinuation of NSAIDs, if possible. It is also essential the early coordination of care among medical, intensive care unit, surgical and radiologist teams, allowing to take appropriate decisions without dangerous delays.

### Bleeding

Peptic ulcer bleeding is a major clinical problem in the emergency setting, in Western countries. The first priority in patient management is correcting fluid losses and restoring the hemodynamic stability. High-dose of intravenous PPIs therapy (80mg in bolus followed by 8mg/h in continuous-infusion for 72 hours) initiated prior to endoscopy, is recommended, because this treatment significantly reduces the rates of ulcers with high-risk stigmata of recent hemorrhage, the need for endoscopic hemostasis and promotes rapid healing [38-40].

Endoscopic therapy has generally been recommended as the first-line of treatment, for upper gastrointestinal bleeding and it should be performed within the 24 hours of the patient admission. It has been shown to reduce further bleeding (OR=0.38; 95% CI, 0.32-0.45); need for surgery (OR=0.36; 95% CI, 0.28-0.45) and the global mortality (OR=0.55; 95% CI, 0.40-0.76). Endoscopic therapy can be divided into injection therapy, which is the oldest technique and usually involves the use of epinephrine with addition of a second agent; mechanical methods with clips and thermal procedures with argon plasma coagulation and bipolar probes [40,41].

Only a minority of patients with bleeding ulcers would require surgical treatment. The indications for emergency surgery include the repeated fail of endoscopic therapy, persistent hemodynamic instability despite resuscitation measures, recurrent bleeding after a second attempt at endoscopic treatment and continued high transfusion requirements. Under these conditions and for some cases, an alternative to surgery is angiography and this procedure may be considered in patients at high risk of surgery.

### Perforation

The perforations are more usual in duodenal, than in gastric ulcers (60 *vs.* 40%), mainly in elderly, and patients with a previous history of heavy alcohol consumption, highly tobacco users and/or NSAIDs intake. In these cases, surgical treatment is indicated. However, in patients with penetrating ulcers, may initially attempt a conservative medical treatment (nasogastric tube, fluid intravenous, parenteral nutrition and broad-spectrum antibiotics) with close monitoring, and if worsening of patient´s status, surgery must be performed [29].

### Gastrointestinal obstruction

This complication should be initially managed with medical treatment measures (nasogastric tube for decompression, intravenous fluid, PPIs to decrease gastric secretion and promote ulcer healing, *H. pylori* eradication). In many cases, these measures can reverse the obstruction by reducing the edema and spasm associated with the lesion. Endoscopic balloon dilation may be attempted if there no response with drug therapy and the healing process has conditioned a severe stenosis [42]. Surgery is the last resort if no improvement is achieved, with either pharmacological and/or endoscopic treatments [29].

### References

1. Goh KL, Chan WK, Shiota S, Yamaoka Y. Epidemiology of Helicobacter infection and public health implications. Helicobacter. 2011; 16: 1-9.

2. Wang AY, Peura DA. The prevalence and incidence of Helicobacter pylori-associated peptic ulcer disease and upper gastrointestinal bleeding throughout the world. Gastrointest Endosc Clin N Am. 2011; 21: 613-635.

3. Chen MY, He CY, Meng X, Yuan Y. Association of Helicobacter pylori babA2 with peptic ulcer and gastric cancer. World J Gastroenterol. 2013; 19: 4242-4251.

4. Malfertheiner P, Selgrad M, Bornschein J. Helicobacter pylori:clinical management. Curr Opin Gastroenterol. 2012; 28: 608-614.

5. Peleteiro B, Bastos A, Ferro A, Lunet N. Prevalence of Helicobacter pylori infection worldwide: a systematic review of studies with national coverage. Dig Dis Sci. 2014; 59: 1698-1709.

6. Calvet X, Ramirez Lázaro MJ, Lehours P, Mégraud F. Diagnosis and epidemiology of Helicobacter pylori infection. Helicobacter. 2013; 18: 5-11.

7. Lee YY, Mahendra Raj S, Graham DY. Helicobacter pylori infection--boom or a bane: lessons from studies in a low-prevalence population. Helicobacter. 2013; 18: 338-346.

8. Tytgat GN. Etiopathogenic principles and peptic ulcer disease classification. Dig Dis. 2011; 29: 454-458.

9. Kanizaj TF, Kunac N. Helicobacter pylori: future perspectives in therapy reflecting three decades of experience. World J Gastroenterol. 2014; 20: 699-705.

10. Shiota S, Suzuki R, Yamaoka Y. The significance of virulence factors in Helicobacter pylori. J Dig Dis. 2013; 14: 341-349.

11. Patel PA, Fleisher LA. Aspirin, clopidrogel and the surgeon. Adv Surg. 2014; 48: 211-222.

12. Sostres C, Gargallo CJ, Lanas A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. Arthritis Res Ther. 2013; 15: S3.

13. Gigante A, Tagarro I. Non-steroidal anti-inflammatory drugs and gastroprotection with proton pump inhibitors: a focus on ketoprofen/omeprazole. Clin Drug Investig. 2012; 32: 221-233.

14. Horrocks JC, De Dombal FT. Clinical presentation of patients with "dyspepsia". Detailed symptomatic study of 360 patients. Gut. 1978; 19: 19-26.

15. Pounder R. Silent peptic ulceration: Deadly silence or golden silence? Gastroenterology. 1989; 96: 626-631.

16. Masclee GM, Valkhoff VE, Coloma PM, de Ridder M, Romio S. Risk of Upper Gastrointestinal Bleeding From Different Drug Combinations. Gastroenterology. 2014; 147: 784-792.

17. Lanas A, García-Rodríguez LA, Polo-Tomás M, Ponce M, Alonso-Abreu I. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. Am J Gastroenterol. 2009; 104: 1633-1641.

18. Holvoet J, Terriere L, Van Hee W, Verbist L, Fierens E. Relation of upper gastrointestinal bleeding to non-steroidal anti-inflammatory drugs and aspirin: A case control-study. Gut. 1991; 32: 730-734.

19. Wallace JL, Mc Knight W, Reuter B, Vergnolle N. NSAID-induced gastric damage in rats: Requirement for inhibition of both cyclooxygenase 1 and 2. Gastroenterology. 2000; 119: 706-714.

20. Rodriguez LAG, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet. 1994; 343: 769-772.

21. Iwakiri R, Higuchi K, Kato M, Fujishiro M, Kinoshita Y. Randomised clinical trial: prevention of recurrence of peptic ulcers by rabeprazole in patients taking low-dose aspirin. Aliment Pharmacol Ther. 2014; 40: 780-795.

22. Gunshefski L, Flancbaum L, Brolin RE, Frankel A. Changing patterns in perforated peptic ulcer disease. Am Surg. 1990; 56: 270-274.

23. Feliciano DV, Ojukwu JC, Rozycki GS, Ballard RB, Ingram WL. The epidemic of cocaine-related juxtapyloric perforations: with a comment on the importance of testing for Helicobacter pylori. Ann Surg. 1999; 229: 801-804.

24. Norris JR, Haubrich WS. The incidence and clinical features of penetration in peptic ulceration. JAMA. 1961; 178: 386-389.

25. Ellis H. The diagnosis of benign and malignant pyloric obstruction. Clin Oncol. 1976; 2: 11-15.

26. Johnson CD, Ellis H. Gastric outlet obstruction now predicts malignancy. Br J Surg. 1990; 77: 1023-1024.

27. Banerjee S, Cash BD, Dominitz JA, Baron TH, Anderson MA. The role of endoscopy in the management of patients with peptic ulcer disease. Gastrointest Endosc. 2010; 71: 663-668.

28. Garza-González E, Perez-Perez GI, Maldonado-Garza HJ, Bosques-Padilla FJ. A review of Helicobacter pylori diagnosis, treatment, and methods to detect eradication. World J Gastroenterol. 2014; 20: 1438-1449.

29. Feldman M, Friedman SF, Brandt LJ. Sleisenger and Fordtran´s Gastrointestinal and Liver Disease. Treatment of peptic ulcer disease. Philadelphia. Saunders Elsevier. 2010; 869-886.

30. Wolfe MM, Sachs G. Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome. Gastroenterology. 2000; 118: S9-S31.

31. Reimer C. Safety of long-term PPI therapy. Best Pract Res Clin Gastroenterol. 2013; 27:443-454.

32. Wedemeyer RS, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: An update. Drug Safe. 2014; 37: 201-211.

33. Agewall S, Cattaneo M, Collet JP, Andreotti F, Lip GYH. Expert position paper on the use of proton pump inhibitors in patients with cardiovascular disease and antithrombotic therapy. Eur Heart J. 2013; 34: 1708-1715.

34. Malfertheiner P, Megraud F, O´Morain CA, Atherton J, Axon ATR. Management of Helicobacter pylori infection. The Maastricht IV/Florence Consensus Report. Gut. 2012; 61: 646-664.

35. Van der Woude CJ, Metselaar HJ, Danese S. Management of gastrointestinal and liver diseases during pregnancy. Gut. 2014; 63: 1014-1023.

36. Cardaropoli S, Rolfo A, Todros T. Helicobacter pylori and pregnancy-related disorders. World J Gastroenterol. 2014; 20: 654-664.

37. Alhazzani W, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ. Proton Pump Inhibitors versus Histamine 2 Receptor Antagonists for Stress Ulcer Prophylaxis in Critically Ill Patients: A Systematic Review and Meta-Analysis. Crit Care Med. 2013; 41: 693-705.

38. Sreedharan A, Martin J, Leontiadis GI, Dorward S, Howden CW. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. Cochrane Database Syst Rev. 2010; 7: CD005415.

39. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol. 2012; 107: 345-360.

40. Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. Clin Gastroenterol Hepatol. 2009; 7: 33-47.

41. Cook DJ, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. Gastroenterology. 1992; 102: 139-148.

42. Cherian PT, Cherian S, Singh P. Long-term follow-up of patients with gastric outlet obstruction related to peptic ulcer disease treated with endoscopic balloon dilatation and drug therapy. Gastrointest Endosc. 2007; 66: 491-497.

Austin J Gastroenterol - Volume 2 Issue 5 - 2015
**ISSN : 2381-9219** | www.austinpublishinggroup.com


**Citation:** Lauret ME, Rodriguez-Peláez M, Pérez I and Rodrigo L. Peptic Ulcer Disease. Austin J Gastroenterol. 2015; 2(5): 1055.