Advances in the pharmacotherapeutic management of refractory peptic ulcers

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Abstract

Introduction: Refractory peptic ulcer is now a rare disease since most peptic ulcers heal with appropriate treatment with proton pump inhibitors (PPIs) and/or *Helicobacter pylori* eradication.

Areas covered: The most frequent cause of apparent refractoriness is lack of adherence to treatment. Persistence of *H. pylori* infection, use or abuse (often surreptitious) of high dose non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin (ASA) are the two major causes of true refractory ulcers. There is a growing number of peptic ulcers which are not linked to either NSAIDs or *H. pylori* infection. Refractoriness in these ulcers can be linked to gastric acid hypersecretion, rapid PPI metabolization, ischemia, chemo-radiotherapy, immune diseases, more rarely to other drugs or be fully idiopathic. Treatment of the cause of the ulcer, if known, is essential. This review is based on pertinent publications retrieved by a selective search in PubMed, with particular attention to refractory peptic ulcer.

Expert opinion: High-dose PPI or the new potassium competitive acid blocker or the combination of PPIs with misoprostol can be recommended in these cases. Other more experimental treatment such the topical application of platelet- rich- plasma, or mesenchymal stem cells have also been suggested. Surgery is the last option, but there is no guarantee of success, especially in NSAID or ASA abusers.

Keywords: Peptic ulcer, refractory peptic ulcer, *Helicobacter pylori*, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin (ASA).

Article highlights

- Refractory peptic ulcers are now a rare entity if treated appropriately, but at the same time, they represent an enormous challenge in clinical practice.

- When facing patients with refractory peptic ulcer, adherence to treatment must be checked (PPI and/or *H. pylori* eradication) because it is the main cause of "false" refractory peptic ulcer.

- NSAIDs or high doses of ASA have been pointed out as the main causes of ulcer refractoriness. Sometimes their consumption is surreptitious.

- Refractory peptic ulcers which are not associated to *H. pylori* or NSAID/ASA use may be due to a diverse number of potential causes that need to be identified. Some of theses causes include use of other drugs (biphosphonates, clopidogrel or chemotherapeutic agents), gastric acid hypersecretion, anastomotic ulcers after bariatric surgery or ischemic ulcers. The identification of factors that determine ulcer refractoriness is essential to make a rational approach to treatment.

- When a reason to explain peptic ulcer refractoriness is not found, different therapeutic approaches can be followed. Increasing the dose of t h e PPI, prescription of the new potassium competitive acid blocker or the combination of these acid antisecretory drugs with misoprostol can be a rational approach.

- New therapies like the use of growth factors or the use of stem cells have been tested in experimental animal models of NSAID induced gastric ulcers showing very promising results, but they can be regarded as still experimental.

- Surgery must be the last option since there is no guarantee of therapeutic success, especially if NSAID or ASA abuse is the cause.

1. Introduction

Peptic ulcer refers to the injury of the gastrointestinal mucosa (usually mucosa of stomach and duodenum, but they can also be located in oesophagus or Meckel's diverticulum) due to acid and pepsin. Peptic ulcer is the most frequent cause of upper gastrointestinal bleeding.

Helicobacter pylori infection and use of non-steroidal anti-inflammatory drugs (NSAIDs) are the main causes of peptic ulcer, both gastric and duodenal ulcers [1]. However, only few people with these etiological factors develop peptic ulcer disease throughout their life.

There is a growing increase in the incidence of idiopathic ulcers not related to either *Helicobacter pylori* infection or NSAID/ASA use. This increase is of concern since they seem to be associated with higher mobidity and mortality [2]. Approximately, 20% of peptic ulcer disease are now *Helicobacter pylori*, NSAIDs and ASA negative in some countries, although the actual prevalence is actually unknown [3]. Patients with idiopathic bleeding peptic ulcers have and increased risk of recurrent ulcer complication and mortality, contrary to the low incidence of. recurrent ulcer bleeding in patients with *Helicobacter pylori* ulcer who received eradication therapy (13% in twelve months vs 2,5% in twelve months) [4].

1.1 Methods

Based on this, the present manuscript aimed to review the literature by a selective search in PubMed between the years 1995 and 2022 with particular attention to refractory peptic ulcer, its management, and new therapies in this field.

2. Management of peptic ulcer

The treatment of peptic ulcer is based on the eradication of *Helicobacter pylori* if the infection is present, as well as the use of antisecretory drugs, namely proton pump inhibitors (PPIs).

These two treatments have improved considerably the management of peptic ulcer. For example, complications related to peptic ulcer disease (like upper gastrointestinal bleeding, perforation, stenosis etc.) have decreased in the last decades. These factors, together with the therapeutic success of endoscopy therapy and radiological intervention in patients with acute peptic ulcer bleeding has reduced considerably the need for surgery in these patients [5].

Treatment of *Helicobacter pylori* has became a challenge because of the development of antibiotic resistance. Now, first line therapy should be based on local prevalence of antibiotic resistance. In 1990s, standard therapies based on PPIs and two antibiotics achieved rates of 90% *Helicobacter pylori* eradication, but today less than 70% of *Helicobacter pylori* eradication is acieved woth this therapy [6,7].

Bismuth-containing quadruple therapy for fourteen days (bismuth salt, PPI, tetracycline, metronidazole) or non-bismuth quadruple therapy for fourteen days (PPI, clarithromycin, amoxicilin and metronidazole) are now the standard first-line therapies. With these two therapies eradication rates of more than 90% are being achieved [7].

More than 85% of NSAID or ASA-associated ulcers heal with PPI therapy taken for 6—8 weeks irrespective of *Helicobacter pylori* eradication, although if present it should be also treated. It is important to keep in mind that healing could be delayed in patients that continue using these drugs. Therefore, NSAID and ASA use should be avoided in patients with active peptic ulcer and a new endoscopy should be performed to confirm healing [1].

3. Refractory peptic ulcer

3.1 Definition

Refractory peptic ulcers are defined as those that does not heal after eight to twelve weeks of conventional therapy. Refractory peptic ulcers can also be considered any ulcere which has complications despite receiving appropriate treatment. However, recurrent peptic ulcers are considered those that reappear after healing [8].

3.2 Epidemiology

The actual rate of frequency of refractory ulcer is not well known, although with current therapies (PPIs and *H. pylori* eradication) the rate of ulcers that do not heal is much lower than years ago (in the eighties and nineties of the former century), when the capacity of acid inhibition with antacids and H-2 receptor antagonists was more limited.

Today if appropriately treated, the rate of either gastric or duodenal ulcer healing after 6-8 weeks of therapy is over 90% [7] . However, the decrease in both *H. pylori* and NSAID/ASA-associated ulcers is being accompanied by an increase in the incidence of idiopathic peptic ulcers which show more refractoriness and high recurrence incidence. For example, according to Kanno *et al.*, the incidence of ulcer recurrence in patients with *H. pylori* -negative NSAIDs-negative idiopathic peptic ulcers was 13,9% versus 2,1% in patients with simple H. pylori ulcers [9]. Other studies how similar results, Hung *et al*. [4] reported that the probability of recurrent ulcer complications during 12 months was 13.4% in patients with idiopathic ulcers and 2.5% in those with *H. pylor*i ulcers with eradication therapy. Moreover, Wong *et al.* [2] reported that the incidence of recurrent bleeding in these patients was 25.2% (and 3.0% in patients with simple *H. pylori* ulcer) in a 7 year-long prospective cohort study. Related to healing rates, Goldstein *et al.* reported that *H. pylori* negative patients were less likely to heal during 8-week treatment with PPI than *H. pylori* positive patients (87% vs 93%) [10].

3.3 Causes of refractoriness and pathogenic factors

3.3.1 NSAID or ASA abuse

The use, and abuse, of NSAIDs is a cause of peptic ulcer refractoriness, several studies have confirmed that NSAIDs or ASA use are behind the absence of healing of peptic ulcers even with high dose PPIs [10]. Often, these patients may deny their intake, because either they are not aware of it, or its consumption is surreptitious (especially ASA abuse). NSAID or ASA use must always be searched and investigated even with objective testing (detection of salicylates in urine, platelet COX activity, levels of NSAIDs in blood, etc.) in patients with refractory ulcers [11].

Other risk factors have been described as significantly associated with refractoriness peptic ulcer, including an early onset of peptic ulcer, duration of ulcer history, number of relapses, or smoking but only NSAIDs/ ASA and frequency of relapses have been confirmed as independent risk factor for refractory peptic ulcer in multiple regression analysis [12].

According to this study, NSAID and ASA use or *Helicobacter pylori* infection could be the etiopathogenic factors involved in refractoriness in more than 75% of all patients with refractory peptic ulcer, although these two factors were not apparently involved in the remaining proportion of patients [12].

3.3.2 Lack of adherence to treatment and Helicobacter pylori persistence:

Lack of adherence is probably the most frequent cause of "false" refractory peptic ulcers.

*Helicobacter Pylor*i treatment is complex, and patients may fail to comply with the full regimen and the 14 days treatment. Adherence must be checked if treatment has failed after six to eight weeks. A new test for *H. pylori* must be performed at least one month after the last dose of antibiotic taken.

According to Malfertheiner *et al* [7], eradication of *Helicobacter pylori* achieves rates of healing of more of 90%, both in gastric and duodenal peptic ulcers. In those patients in whom the treatment has failed, adherence must be investigated. It is also important to follow the right procedures for re-testing and avoid false negative *Helicobacter pylori* tests.

Some medications, such as PPIs, bismuth salt or even antibiotics reduce temporarily, but do not eliminate, *H. py*lori from the gastric mucosa. If the test is performed earlier than recommended after the last dose of these medications (10 days for PPIs, one month for antibiotics) the test may provide a false negative result [7].

3.3.3 Smoking

Smoking is considered a controversial risk factor. Tobacco reduces prostaglandins synthesis, decreases the function of gastric mucosal barrier and blood flow to gastric mucosa. Also, it increases acid secretion and decreases mucosal bicarbonate secretion. All these factors may delay healing of peptic ulcers [13,14].

For example, González-Pérez *et al.* identified 3914 patients with uncomplicated peptic ulcer disease between 1997-2005. Smoking was more prevalent between patients with uncomplicated peptic ulcers than in patients who did not develop peptic ulcer (95% CI OR 1.9 (1.72-2.10)). Also, the same association was identified in former smokers (95% CI OR 1.3 (1.15-145)) [15].

Patients with refractory peptic ulcer usually smoked more than patients without this refractory ulcer, but these differences do not reach differences statistically significant and smoking not always emerges as an independent significant factor [12,16].

3.3.4 Acid hypersecretion or inappropriate acid suppression therapy

A higher basal gastric acid secretion has been postulated as a cause of refractory gastric ulcer, but this was not apparently a determinant because those levels are easily suppressed by standard antisecretory therapy in patients with duodenal ulcer [12]. In general patients with duodenal ulcers have higher levels of gastric acid secretion. Standard PPI therapy is enough to heal the majority of these type of ulcers. In cases where healing is not achieved, lack of adherence to treatment must be suspected [1]. In any case, acid hypersecretion that is not appropriately suppressed by antisecretory drugs may be one of the causes of refractoriness.

Gastric acid hypersecretion can be seen in patients with idiopathic peptic ulcers, and more rarely in patients with Zollinger-Ellison syndrome, Multiple endocrine symdrome I (MEN I) or retained antrum syndrome after surgery [17].

3.3.5 Other causes

In some refractory ulcers, neither NSAIDs nor ASA seem to be involved, but other drugs, although much less frequently involved, have also been described.

Clopidogrel, bisphosphonates, some chemotherapic agents or mycophenolate have been described in the literature as ulcerogenic and their use can delay healing [15].

Also, abdominal radiotherapy or chemoembolization have been described as potentially involved in ulcer refractoriness [15]. These latter causes are characterized above all by a worse response to treatment with PPIs. This may indicate that gastroduodenal ulceration is not only acid dependent, because some refractory ulcers heal after drug discontinuation, which means that other factors have to play a role [16].

In the Table 1 we explain main causes of peptic ulcer refractoriness.

3.4. Symptomatology

Peptic ulcer disease can cause different symptoms depending on location. Patients with gastric ulcers usually have postprandial abdominal pain, nausea and vomiting and can have weight loss. In the case of duodenal ulcers, patients usually have nocturnal abdominal pain that improve after meals. Elderly people usually have milder symptoms [1].

Refractory peptic ulcers usually are atypical, multicentric, have poorly defined margins, commonly change site and are more predisposed to have complications (like bleeding or stenosis), besides being more refractory [8,9,10,16,18]. These characteristics have been well described in patients with aspirin abuse [16,18]. The presence of multiple ulcers and atypical locations must rise the suspicion that we are not in front of H. pylori related peptic ulcer.

Refractory peptic ulcers can complicate and manifest as melena or haematemesis. Perforation starts with sudden onset of intense pain in the upper abdomen [18].

4. Management of refractory peptic ulcer and Prevention:

4.1. Check adherence to treatment and *Helicobacter pylori* eradication and/or use/abuse of NSAIDs/ ASA.

Prevention of peptic ulcer refractoriness requires the prescription of an appropriate treatmentand a good adherence of patients to the prescribed treatment.

H. pylori infection must be searched and treated according to the last guidelines or recommendations based on local antibiotic resistance [6,7]. Eradication of the infection must be confirmed, especially in absence of healing or recurrence. However, there are studies reporting that peptic ulcers can reappear after correct therapies [19]. Lanas *et al. r*eported that a small but significant number of patients (16.6%) do not heal or have a rapidly recurrence after correct eradication treatment [16]. Usually, classic chronic duodenal or gastric *H. pylori*-positive gastric or duodenal ulcers tend to reappear at the same site [18]. The reasons for this reappearance are unclear, but ulcer healing is related to acid inhibition [16] which means that most of these ulcers may remain asymptomatic with low doses of maintenance treatment with PPIs [18].

In case of ulcer refractoriness, as important as confirming *Helicobacter pylor*i eradication, is to perform and active search for drug use, especially NSAIDs and ASA. Standard doses of PPI heal both gastric and duodenal ulcers even with active NSAID or ASA (often low dose) use. In cases of refractory peptic ulcers due to these drugs, the search may reflect the use of high doses, which sometimes is surreptitious and must require objective testing with the presence of drugs in blood or urine [11,12,16].

4.2 Doubling PPI dose

Doubling PPI dose could be a strategy if an ulcer does not heal, but there is no evidence that this strategy would be better that standard dose of PPI. Long term PPI therapy, although is recommended, did not prove better clinical outcomes [11,20]. There is a relationship between healing and antisecretory power. Increasing gastric pH > 4 at least 16 hours per day improve healing rates [21].

Calvet and Gomollón considered that the majority of patients with peptic ulcer that did not heal in six to eight weeks could achieve it if PPI dose was doubled [21]. It is unclear why these ulcers do not heal with standard dose of PPI. Genetic factors and other external factors could be responsible of these differences. CYP2C19 is responsible for PPIs metabolism. This cytochrome, which is encoded by a polymorphic gene, could trigger slow and fast metabolizers of PPIS [22]. Fast metabolizers may require higher doses of PPI.

Other studies have postulated that rates of acid inhibition is more powerful in patients who take PPIs and have *Helicobacter pylori* infection than patients who take PPIs but *Helicobacter pylori* is not present. This could be explained because eradication of *Helicobacter pylori* reduces the capacity of PPIS to increase the gastric pH. This fact has been shown in different studies, and it is explained because of the production of ammonia by H. *pylori. A*mmonia increase intragastric pH during treatment with antisecretory drugs but disappear when the bacteria is eliminated [23,24]. Iijima e*t al*. reported that the gastric acid secretion level in *H. pylori*-negative subjects was statistically significantly higher than in *H. pylori*-positive subjects over a 20-year period in Japan [25]. However, these studies have to be taken with caution, because in the group where PPI was less effective (*Helicobacter pylori* negative group) patients had an increased consumption of NSAIDs compared the other group [9].

New Maastricht VI/ Florence consensus [7] says the use of high-dose PPI twice daily increases the efficacy of triple therapy, but it remains unclear whether high dose PPI twice daily can improve the efficacy of quadruple therapies, which are now the standard first-line therapies.

4.3. Rule out other causes

It is important to bear in mind that in addition to the above mentioned causes, other more rare etiologies may be present.

Endocrine tumors such as gastrinomas within the Zollinger Ellison or MEN I syndromes, a rare

but important cause of refractory gastroduodenal ulcers [26]. Peptic ulcers will not cure until tumors are controlled or removed.

Infrequent causes of refractory peptic ulcer include the presence of intestinal ischemia in vasculopathic patients with involvement of two abdominal arterial trunks [13]. In these cases, the symptoms of abdominal ischemia, risk factors and imaging tests would be essential for an appropriate diagnosis and treatment. These ulcers will not heal with PPIs, but through arterial revascularization.

With the rise of bariatric surgery in obesity, the incidence and prevalence of refractory peptic ulcer in these patients have increased. Approximately 0.6-25% of patients undergoing bariatric surgery(gastric bypass with Y of Roux) will suffer from peptic ulcer [27]. These ulcers are called "isquemic ulcer" or "anastomotic ulcer" or "marginal ulcers". Only two thirds of patients who develop them respond to medical treatment, while up to one third require reconstructive surgery [28,29]. In the case of Billroth II gastrectomy patients, a small proportion of antral mucosa with gastrin- producing cells may remain in the proximal duodenal portion. The alkaline environment stimulates these cells, which increase their gastrin production and therefore the formation of ulcers in these cases. The "Retained antrum syndrome" will need surgical removal of the excluded portion of the antrum to cure [16].

4.4 The role of surgery in Refractory peptic ulcer

The role of surgery in refractory peptic ulcers is not well established and will depend on the cause of refractoriness [7]. Surgery is currently indicated in those ulcers that have complications which can not be treated by other means. Also, surgery can be recommended in those intolerant patients to conventional treatment or those with recurrent ulcers despite adequate medical treatment or patients with refractory peptic ulcers.

The types of surgical treatment include partial gastrectomy with associated vagotomy, truncal vagotomy with drainage with pyloroplasty or gastrojejunostomy, or supraselective vagotomy. The advantage of this last technique is the low rate of side effects, but recurrence of peptic ulcer is more likely. On the other hand, while in the first two surgeries, the recurrence is much lower, the probability of secondary effects such as diarrhea or dumping is greater [30].

The goal of surgery is to reduce the level of gastric acid secretion and/or remove the actual ulcer, especially if an ischemic component is suspected.

Surgery does not ensure post-surgical ulcer can reappear. In fact, in patients with continued aspirin abuse, recurrent ulceration is the rule and these patients should be excluded at elective ulcer surgery because aspirin ulceration is incurable by gastric surgery [31].

5. New therapies in refractory peptic ulcer

New medical treatments are being developed in this field. The goal of these new medical treatments is to reduce surgical interventions. The increased number of idiopathic ulcers associated with *Helicobacter pylori* infection or NSAID treatment is of concern since they are associated with higher rates of recurrence and refractoriness.

According to Takeshi Kanno *et al*., the proportion of refractory peptic ulcer in Japan was 12% of the total when they conducted their study between April 2012 and March 2015, which was fivefold higher of Japanese reports during the 2000s [9,32]. Vonoprazan is a potassium competitive acid blocker (Murakami K. *et a*l), with increased antisecretory potency compared to other PPIs. It inhibits the proton pump activity of cytoplasmic vesicles and secretory canaliculus, resulting in a stronger and more sustained inhibition of gastric acid secretion than conventional PPIs [33,34]. It is expected to be an alternative option in gastroesophageal diseases where conventional PPIs could fail.

Vonoprazan combined with amoxicillin and clarithromycin or metronidazole as a first or second line treatment of *Helicobacter pylori* infection, achieved eradication rates of more than 90% in *Helicobacter pylori* positive peptic ulcers, which were higher than those obtained with PPIs [33].

In a Phase-3 trial, high healing rates were achieved with approved dosing regimen of Vonoprazan (20 mg for six weeks in duodenal ulcers and 8 weeks in gastric ulceeres): 93.5% in gastric ulcers and 95.5% in duodenal ulcers. Refractoriness was defined as unhealed ulcers after six or eight weeks of treatment depending on the location of the ulcer [34]. Sugawara K *et al.* developed and observational study in Japan. In this study, overall healing rates were lower than expected and founded in Phase-3 trial: Healing rate for *H. Pylori* positive ulcers was 93,5%, while it was inferior in ulcers *H. Pylori* and NSAIDs negative: 81,2% [34]. More studies are needed to figure out if healing rates will be higher with long-term Vonoprazan

treatment.

Murakami K *et al.* described that in refractory peptic ulcers greater acid suppression was not enough to obtain higher healing rates because healing rates were similar with Vonoprazan and conventional PPIs [33]. They also found that peptic ulcers in patients taking chronic NSAIDs could be refractory to long-term treatment with both PPIs and vonoprazan [33].

Other treatments or molecules have been proposed recently. New therapies based in natural products have became an alternative. For example, flavonoids have a gastroprotective effect through different mechanisms. They can increase mucus and the activity of SOD and CAT enzymes, which let them antioxidants properties. They also can decrease proinflamatory cytokines and have antisecretory and anti- *H. Pylori* action. They could become a complementary treatment in the future in refractory peptic ulcer or helping to avoid recurrence [35].

Monoterpenes are another option. Monoterpenes are a variety of terpenes that contain two isoprenes in their molecule. They have multiple pharmacological actions like wound healing, anti-ulcerogenic, antioxidant, antitumour, antimicrobial and anti-inflammatory properties [36].

Other studies have described the role of Benzimidazole derivatives in diseases related to *H. Pylori.* They have antibacterial, anti-inflammatory, anti-ulcerative properties [37]. Therefore, it could be a good opportunity to develop new drugs based on these molecules.

The healing of peptic ulcer is a multistep and complex process, which includes inflammation during the initial process, followed by a period of cell proliferation, re-epithelization and angiogenesis [38]. It has been postulated that stem cells derived from bone marrow could help in this process [39]. Mesenchymal stem Cells or Mensenchymal Stromal cells (MSC) are multipotent progenitors that have the capacity for self-regeneration and proliferation [40]. These MSC attach to the endothelial cells and travel to damaged area, where they have the ability to differentiate into certain cell types (including endothelial cells) and secrete anti-apoptotic and angiogenic factors [41]. For example, adipocyte-derived stem cells secrete VEGF, TGF- β, FGF and HGF, which inhibit inflammation and enhance angiogenesis [38].

In the future, stem cells could be a treatment for refractory peptic ulcers that do not respond to usual treatments or ulcers that reappear after an appropriate treatment. Adipose-derived mesenchymal stem cells are available in large quantities with minimal invasive intervention [38].

6. Conclusion

The identification of factors that determine ulcer refractoriness is essential to make a rational approach to treatment. Lack of adherence to correct treatment (PPI or *Helicobacter pylori* eradication treatment) and NSAID/ASA abuse are the main causes of apparent or true peptic ulcer refractoriness. Nevertheless, there are other causes that must be taken into consideration now that the incidence of idiopathic peptic ulcers unrelated to NSAID or *H. pylori* infection is growing. New therapies and approaches should be developed for ulcers where the cause of refractoriness is not found.

7. Expert Opinion

Peptic ulcer is one of those GI pathologies whose importance, based on its incidence and prevalence within the population, has been declining in the last decades. In the 20th century, dealing with patients suffering from peptic ulcer diseases was an important part of the workload of gastroenterologists and surgeons. The lack of effective medical treatments associated with a significant proportion of refractory peptic ulcers and/or rapid recurrence after healing, and also with complications such as bleeding or perforation, which determined that many patients were submitted for more definitive surgical treatment [42].

Today, refractory peptic ulcers are a rare entity if treated appropriately, but at the same time, they represent an enormous challenge in clinical practice. The incorporation of more potent acid inhibitors such H2RAs and overall PPIs, reduced the incidence of refractory peptic ulcers considerably [43]. Moreover, the discovery of the role of *Helicobacter pylori* in peptic ulcer disease changed the natural history of peptic ulcers and reduced considerable, not only the rate of recurrence of this disease, but the incidence of refractory peptic ulcers what was of the utmost importance.

Nevertheless, despite these important advances, still there are a number of peptic ulcers that are resistant to heal. Refractory peptic ulcers can be sorted out in two separated groups. The first one is the group of refractory peptic ulcers still linked to the two major causes of peptic ulcers, namely NSAID/ASA treatment, *Helicobacter pylori* infection or both. The other group includes patients not linked to NSAID/ASA or *H. pylori* infection. Heavy smoking has been a factor also associated with ulcer refractoriness, but its role was mainly seen before the incorporation of PPIs and *H. pylori* eradication in our therapeutic armamentarium [16].

When facing patients with peptic ulcers that do not heal with standard therapy, the first step is to confirm adherence to treatment (PPI and/or *H. pylori* eradication). This is the main cause of apparent or false refractoriness. Persistence of H. pylori infection is one of the major causes of peptic ulcer recurrence, but also lack of H. pylori eradication has been linked with peptic ulcer refractoriness. A confirmatory test of *H. pylori* eradication [1,7,12] is not commonly performed outside the gastroenterology environment. Therefore, this should be the next step in patients whose ulcers do not heal after a first, second or third course of *H. pylori* treatment. A molecular PCR analysis aimed to detect the presence of *H. pylori* in the gastric tissues may be warranted in some cases.

Use, especially abuse of NSAIDs or high doses of ASA has been pointed out as on the main causes of ulcer refractoriness [12,18]. Most peptic ulcers will still heal with PPIs despite patients may keep taking NSAIDS at standard dose. In the same way, peptic ulcers in patients taking low- dose aspirin will heal with standard doses of PPI and even H2RAs [44]. However, the use of high dose of these compounds may prevent peptic ulcer healing since they reduce the gastric mucosal defense mechanism and the healing process [18]. Today, these compounds can be obtained over- the-counter without the necessary supervision of medical care providers. Often, patients may not confess this abuse and its detection need objective testing by routine analysis of the presence of these compounds in blood or urine. Recurrence of peptic ulcer is the norm after surgery in these patients, and therefore they should not be sent for surgery unless they develop a life-threatening complication [31].

Refractory peptic ulcers which are not associated to H. pylori or NSAID/ASA use may be due to a diverse number of potential causes that need to be identified. Drugs such as Olmesartan,

high doses of corticosteroids, crack cocaine use, etc. have been linked to this pathology, but they are extremely rare. More common are refractory peptic ulcers linked to surgery of obesity due to the increased number of these procedure performed worldwide. The pathogenesis behind them seems to be ischemic which implies that they rarely will heal unless we correct this deficit, often with another surgical intervention [28,29]. Other sources of refractory peptic ulcers such those occurring after oncological treatments based on radiotherapy or chemotherapy are easily identified [15]. Different systemic autoimmune diseases or infections with other agents such as cytomegalovirus, mycobacterium tuberculosis, etc. may induce extensive gastritis and ulceration. Healing of those ulcers will require the treatment of the disease in addition to PPI therapy [45].

Gastric acid hypersecretion which exceeds the mucosal defense mechanism is the other major player in this context. One example of this are refractory peptic ulcers associated to tumors such as gastrinomas who have an exaggerated gastric acid hypersecretion. These patients will require very high doses of PPIs or vonoprazan administered each 6-8 hours unless the tumor is removed [46,47].

However, most peptic ulcers not linked to NSAIDs or *H. pylori* will be considered idiopathic, since no other cause could be identified. Most of these idiopathic ulcers are being controlled with PPIs since they exhibit gastric hypersecretion. Those idiopathic peptic ulcers that do not heal with standard doses of PPI will require higher doses or be switched to new compounds such as Vonoprazan, which shows a higher capacity of acid inhibition than most PPIs.

Another approach in this context may be to perform genetic testing to detect rapid metabolizers patients who will need to increase the dose and timing of use of PPIs [22,48].

The identification of factors that determine ulcer refractoriness is essential to make a rational approach to treatment. Still, some refractory peptic ulcers will not have a clear reason to explain the absence of healing. In these circumstances different approaches can be done.

One is to maximize the dose of PPI combined with additional therapies. Combination of PPIs or potassium competitive acid blocker with misoprostol is a rational approach since both types of drugs have shown efficacy on the healing of ulcers and have different mechanisms of action.

The use of growth factors has been used successfully in other type of ulcers (e.g. skin), and this approach have also been tested in peptic ulcers with growth factors derived from platelet-rich plasma from the same patient [49].

Other more sophisticated and recent treatments have been proposed such the use of stem cells. Both bone marrow derived mesenchymal stem cells and adiposed-derived stem cells are multipotent progenitor cells with proliferation and self- egeneration capacity that participate in tissue repair and have immune regulatory properties among other functions [38,41]. They have been tested in various experimental animal models of NSAID-induced gastric ulcers obtaining very promising results [38,41]. This therapy could also be used in refractory ulcers associated to radiation resistant gastrointestinal ulcers [38].Unfortunately, the evidence to support these approaches is limited or absent and some of them must be regarded as purely experimental.

Eventually, surgery will be the last step to treat these ulcers, especially if they develop a complication. However, is important to rule out all potential causes that can be managed with medical treatment, since surgery will no guaranty success or absence of recurrence.

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*This paper refers to new therapies that have been proposed to treat refractory peptic ulcers. Some of them have been tested in experimental animal models or different studies, with very promising, yet experimental results.

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Table 1. Main causes and pathogenic factors of peptic ulcer refractoriness

Use and/or abuse of NSAIDs/ASA	Helicobacter pylori persistence
Lack of adherence to treatment	Use other drugs (biphosphonates, clopidogre chemotherapeutic agents,mycophenolate)
Gastric acid hypersecretion	Gastric acid hypersecretion due to endocrine tumors: Multiple endocrine syndrome (MENI), Zollinger-Ellison
Chemoembolization	Radiotherapy
Retained antrum syndrome after surgery	Anastomostic or isquemic ulcers in patients undergoing bariatric surgery// Billroth II gastrectomy
Smoking*	Intestinal ischemia in vasculopathic patients

* Controversial risk factor.

Figure legends

Figure 1. Algorithm for management of refractory peptic ulcer

Figure 2. Adapted from Lanas A, Remacha B, Esteva F, Sáinz R. Risk factors associated with refractory peptic ulcers. Gastroenterology. 1995 Oct; 109(4):1124-33. It illustrates the role of H. Pylori infection and NSAIDs/ASA abuse in patients with refractory peptic ulcer.

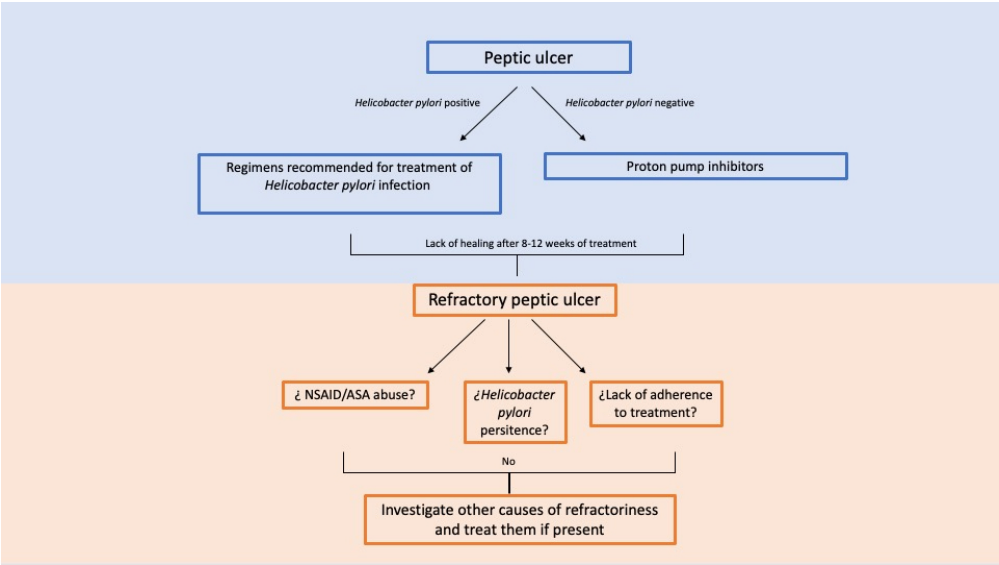

Figure 1. Algorithm for management of refractory peptic ulcer.

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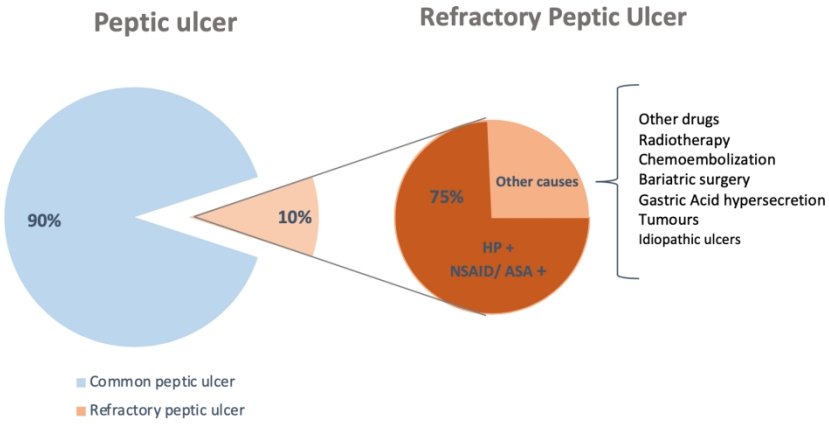

Figure 2. Adapted from Lanas A, Remacha B, Esteva F, Sáinz R. Risk factors associated with refractory peptic ulcers. Gastroenterology. 1995 Oct; 109(4):1124-33. It is shown the role of H. Pylori infection and NSAIDs/ASA abuse in patients with refractory peptic ulcer.

363x196mm (144 x 144 DPI)