Journal of
Biomedical and Biological Sciences

Bereda G, J. Biomed. Biol. Sci. 2022, 1:2

Review Article Open Access

Peptic Ulcer Disease: Definition, Pathophysiology, and Treatment

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Citation: Bereda G. Peptic Ulcer Disease: Definition, Pathophysiology, and Treatment. Journal of Biomedical and Biological Sciences. 2022;1(2):1-10.

Received Date: 9th January, 2022 **Accepted Date: 25th February, 2022** **Published Date: 6th March, 2022**

Abstract

Peptic ulcer can be delineated as the presence of a deep destruction of the mucosa of the stomach and/or duodenum, reaching beyond the muscularis mucosa, specifically to the muscle layer owing to the environmental gastric acid synthesis. Peptic ulcer, also known as stomach ulcer, is a breakage of mucosal lining of stomach, first section of the small intestine and sometimes in the lower esophagus. Caffeine and coffee are ubiquitously considered to antecedent or exaggerate pains, appear to have less consequence. Goals of management are to relieve ulcer pain, heal the ulcer, obviate ulcer recurrence, minimize ulcer-related complications, and eradicate Helicobacter-pylori in Helicobacter-pylori-positive patients.

Keywords: Definition; Pathophysiology; Peptic Ulcer Disease; Treatment

Abbreviations: ASA: Acetylsalicylic acid; COX: Cyclooxygenase; H_2RAs: Histamine type $_2$ receptor antagonists; H_3CO_3: Bicarbonate; Hp: Helicobacter pylori (Hp) NSAIDs: Nonsteroidal anti-inflammatory drugs; Pgs: Prostaglandins; PCN: Penicillin; PPIs: Proton pump inhibitors; PUD: Peptic ulcer disease; RBC: Ranitidine bismuth citrate; ZES: Zollinger-Ellison syndrome

Introduction

Peptic ulcer can be delineated as the presence of a deep destruction of the stomach lining or mucosa and/or duodenum, reaching beyond the muscularis mucosa, specifically to the muscle layer owing to the environmental gastric acid synthesis. The two consummate ubiquitous etiological antecedents are the chronic infection with Helicobacter-pylori (Hp) and the use of NSAIDs, involving of course, the ASA. There are distinctive less ubiquitous antecedents that can cause a PU, which are thought-out together, responsible for < 5% of cases. Zollinger-Ellison syndrome (ZES) or gastronomy is one amid them which is a neuroendocrine tumor, often located at the head of the pancreas or in the duodenal wall, overactive and gastrin secretory [1]. Ageing is claimed to escalate the peril for several gastroduodenal disorders, such as gastric atrophy with intestinal metaplasia, PUD, ulcer bleeding and gastric cancer [2]. The unknown cause peptic ulcer disorders are delineated as a painful sore that is not well-known antecedent or a painful sore seems to arise spontaneously. Peptic ulcers are acid-initiated lesions resulted in the stomach & duodenum described by denuded mucosa with the shortcoming prolonging into the submucosa or muscularis propria. Lesions that do not reach this depth are called erosions [3]. Gastric acid is well characterized as the antecedent of peptic ulcer,

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while H. pylori infection is recognized as the major causative factor in ulcer formation. The bacterium antecedents enliven in the secretion of gastric acid owing to gastritis, and this cycle attributes to erosion of the mucosa and ulcer formation. Furthermore, imbalance between offensive factors (excessive gastric acid, H. pylori, gallbladder fluid, and elevated free radicals) and defensive factors (mucosa, blood fluid, prostaglandins, and antioxidants) perhaps also result in development peptic ulcer [4, 5]. PUD, one of the consummate ubiquitous ulcers, refers to ulcer of the GIT in the region of the stomach. It is explained by more acidity sequencing in mucosal erosions antecedent severe pain and distress. By definition, mucosal erosions should be equal to or exceed 0.5 cm [6]. Peptic ulcers can be broadly classified into gastric or stomach ulcer and duodenal ulcer. Gastric Ulcers occur mainly in the elderly, on the lesser curve. Duodenal ulcers are 4 times common than gastric ulcer. It is distinguished by the consummate ubiquitous symptom i.e.; the epigastric pain happens typically before meals or at night which is relieved by eating or drinking milk [7]. H. Pylori infection or NSAID use alone may not be sufficient to cause peptic ulcer disease. Other factors like genetic and environment factors also contribute. People with DUs are more likely to have family members with duodenal ulcers compared to general population. Distinctive peril factor for advancing an ulcer is use of tobacco in any form like smoking because it escalates the peril of ulcers and impairs the process of healing. Alcohol consumption to some extent also causes the same effect [8].

Pathophysiology

Under normal conditions, duodenal and gastric mucosa integrity is maintained by the mucus-bicarbonate barrier, the neutral pH, and continuous epithelial cell renewal [9, 10]. PGE2 enliven cell proliferation, mucus, and H_3CO_3 secretion, promoting an essential work in mucosa preservation. Distinctive crucial factor in gastric homeostasis is sufficient blood flow. The NO and PGs are accountable for the maintenance of appropriate perfusion to the gastric mucosa, ensuring the delivery of O_2 and nutrients, as well as take-off toxic metabolites, obviating damages to the tissue [11].

Ubiquitous peril factors antecedents for PUD and gastritis involve infection with Helicobacter pylori, and NSAIDs. Less ubiquitous peril factors involve alcohol, smoking, cocaine, severe illness, autoimmune problems, and radiation therapy and Crohn disease amid distinctive [12].

Helicobacter pylori: The mechanisms, through which the Hp favours the advancement of PU, are better known in the duodenal, than in gastric side [13]**.** H. pylori antecedent an inflammatory reaction with neutrophils, lymphocytes, plasma cells, and macrophages within the mucosal layer and antecedent's epithelial cell degeneration and damage. Gastritis is often further severe in the antrum, with little or no inflammation in the corpus. Entire patients resulted to have peptic ulcers should be tested for H. pylori [14]. Inflammation consociated with H pylori infection can sequence in either hypochlorhydria or hyperchlorhydria, [15] and thus ascertain the type of peptic ulcer formed [16, 17].

NSAIDs induced ulcer: There are two chief mechanisms by which NSAIDs antecedent injury to the duodenal and gastric mucosa. On one hand, these medications behave as weak non-ionized acids, that can penetrate into the mucus layer simply, and inside the epithelial cells. Distinctive and consummate indispensable consequence is the capability of cyclo-oxygenase inhibitory enzyme, thereby de-escalating the intracellular concentration of prostaglandins. These play a significant role in maintaining the integrity of the gastroduodenal mucosa function, because of its intramucosal vasodilator outcome maintaining intact the blood flow and secondarily enliven the local production of mucus and H_3CO_3, facilitating the cell turnover and epithelization [18, 19]**.** NSAIDs are broadly used for a variety of situations to support to minimize pain and inflammation; however, multiple users advance GI side effects. NSAIDs responsible for over 90% of all ulcers and approximately 25% of NSAID users will advance PUD [20]. Aspirin users are also twice as likely to advance peptic ulcers as the general population [21]. Distinctive advance a milder level of topical damage, which is seen as mucosal hemorrhages and erosions and are referred to as NSAID

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gastropathy. These multiple small erosions are usually located in the antrum but may also be seen in the body [22]. NSAIDs damage the gastroduodenal mucosa through both systemic and local mechanisms, but the systemic inhibition of constitutively expressed cyclooxygenase 1 (COX-1)-derived prostaglandins are regarded as the main mechanism. Reduced mucosal PG values are consociated with low mucus and H_3CO_3 production, suppression of cell proliferation, and de-escalated mucosal blood flow, which are crucial to maintenance of mucosal integrity. The COX hypothesis is assisted by surveys revealing that coadministration of exogenous Pgs minimizes mucosal injury [23]. COX-2-selective NSAIDs, which spare COX-1, minimize the peril of ulcers [24]. However, this hypothesis does not fully describe the spectrum of mucosal injury. People receiving NSAIDs could have a predominant de-escalate in mucosal Pgs without necessarily advancing gastric lesions. NSAIDs have disparate physicochemical properties and a broad range of pKa values, which responsible for certain distinctive in their toxicity and extent of topical injury [25]. NSAIDs initiate mucosal detriment in the cell through destruction of mucus phospholipids or the cell membrane and by uncoupling of mitochondrial oxidative phosphorylation [26-29].

Stress and diet: Stress owing to serious health challenges such as those needing management in an intensive care unit is well characterized as an antecedent of peptic ulcers, which are termed stress ulcers [30]. Coffee and caffeine are ubiquitously considered to antecedent or exaggerate pains, seem to have less consequences [31]. Skipping of meals permits gastric acid to directly act on surface stomach lining causing irritation which finally influences to gastric ulcers. Gastric ulcers antecedent abdominal pain which aggravates with meals [32].

Smoking and alcohol: Consumption of alcohol and smoking are peril factors. Chronic alcohol disturbs gastric mucosal obstacles by obviating COX 1 receptor enzymes which minimize the secretion of cytoprotective prostaglandin. Cigarette smoking antecedent's decrement of circulating epidermal growth factor and escalate free radical secretion in gastric mucosa [32].

Management of PUD

Management of PUD should include eradication of Helicobacter pylori in patients with this infection. Goals of management are to relieve ulcer pain, cure the ulcer, obviate ulcer recurrence, reduce ulcer-related complications, and eradicate H. pylori in H. pylori-positive patients.

Non-pharmacologic Treatment

Eliminate or reduce psychological stress, reduce use of nonselective NSAIDs (including aspirin), use alternatives for pain relief such as acetaminophen, or COX-2 selective inhibitors, stop cigarette smoking, restrain beverages and foods that antecedent dyspepsia or exacerbate ulcer symptoms example., caffeine, spicy foods, alcohol, and emergency surgery for some patients with bleeding, perforation, or obstruction.

Pharmacological Treatment

The consummate successful groups of medications were those obviating gastric acid production. H_2-receptor antagonists revolutionized management of peptic ulcer, healing ulcers and keeping them in remission when bestowed as maintenance therapy [33, 34]. They were gradually displaced with the further powerful group of acid-inhibitory medications so called proton-pump inhibitors (PPIs), which became applicable in 1989. PPIs are selectively suppressing the H^+ K^+ ATPase of the parietal cell [35]. On the basis that speed of ulcer healing is consociated with level of acid suppression; PPIs became the symbol in ulcer therapy. A 2nd class of medications is directed at reinforcement of the mucosal stumbling block, and has result its preponderance application in protection against NSAIDs and aspirin. Misoprostol, a prostaglandin analogue, has been the consummate broadly used but its application is limited by abdominal side-effects, particularly at higher doses [36]. Sucralfate and bismuth salts also promote ulcer healing by ameliorating mucosal mend. Sucralfate might also act partly by minimizing acid production and inhibiting H pylori infection [37]. Bismuth salts with some intrinsic

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anti-H pylori activity are used in ulcer therapy solely in combination with antibiotics. Cytoprotective medications have been obsolete by further effective therapies. Recent ulcer therapy encloses of Helicobacter pylori eradication in H pylori-positive peptic ulcer and PPI for healing and obviating peptic ulcers initiated by gastronomic medications. A small function exists for medications accelerating mucosal resistance.

Standard Triple Therapy

A 7- to 10-day triple therapy regimen involving of a PPI, amoxicillin 1 g, and clarithromycin 500 mg twice daily has long been the 1st-line therapy to eradicate Helicobacter pylori. First line therapy for H. pylori eradication involves a PPI, clarithromycin and amoxicillin or metronidazole (for PCN-allergic patients) for 7 to 14 days [38]. Eradication of H. Pylori is recommended for H. Pylori-infected patients with PUD and ulcer-related complications. PPI-based triple therapy for 10 to 14 days; PPI once/bid + clarithromycin 500 mg bid + amoxicillin 1 g bid or metronidazole 500 mg bid; primary management of choice for eradicating H. pylori; metronidazole should be substituted for amoxicillin solely in penicillin (PCN) allergic individuals since metronidazole resistance is common. PPI should be taken 30 to 60 minutes before a meal along with the two antibiotics. PPIs functions synergistically with antibiotics to eradicate Helicobacter pylori [39]. Owing to escalating antibiotic resistance, the efficacy of triple therapy has fallen below 70% in many countries. As susceptibility testing is frequently not present in clinical practice, clarithromycin-depend regimens should be avoided when local clarithromycin resistance rates are > 15% [38, 39]. When using clarithromycin-based triple therapy, eradication rates can be escalated with use of high dose PPI and by extending the duration of treatment from seven to 14 days. For descent with high clarithromycin resistance, bismuth-containing quadruple therapy with a PPI, bismuth, tetracycline and a nitroimidazole (metronidazole or tinidazole) for 14 days or PPI, clarithromycin, amoxicillin, and a nitroimidazole for 14 days is the preferred as first line treatment [40]. There have been issues with the cost and availability of tetracycline and the data have been mixed on whether doxycycline can be substituted. The regimens explained above give eradication rates greater than 90%. The regimens involve: (a) PPI in standard dose + clarithromycin 500 mg + amoxicillin 1000 mg each given twice daily (b) PPI in standard dose + clarithromycin 500mg + metronidazole 400 mg, each given twice daily(c) Ranitidine bismuth citrate (RBC) 400mg + clarithromycin 500 mg + amoxicillin 1000mg, each given twice daily (d) RBC 400 mg +clarithromycin 500 + metronidazole 400 mg, each given twice daily. Each of above regimen should be given for 7 days [32]. **Rifabutin triple therapy:** PPI (standard dose twice daily) + amoxicillin (1 g twice daily) +rifabutin (150-300 mg/day) for 10 days.

Sequential Therapy

Sequential therapy is another form of quadruple therapy, which consists of a 5-day dual therapy with a PPI and amoxicillin followed by a 5-day triple therapy with a PPI, clarithromycin, and tinidazole or metronidazole. Overall, the eradication rate of sequential therapy is better than that of 7-day and 10-day triple therapy regimens but not better than the eradication rate of 14-day triple therapy, bismuth-based therapy, and non-bismuth-based concomitant therapy [41, 42] and this treatment is not recommended. Hybrid quadruple therapies combine 10−14 days of dual therapy with PPI and amoxicillin with 7 days of treatment with clarithromycin and metronidazole. **Sequential therapy:** PPI (standard dose twice daily) + amoxicillin (1 g twice daily) for 5 days followed by PPI (standard dose twice daily) + clarithromycin (500mg twice daily) + tinidazole (500mg twice daily) for 5 days. Levofloxacin triple therapy: PPI (standard dose twice daily) + amoxicillin (1g twice daily) +levofloxacin (500mg twice daily) for 10 days.

Bismuth-Based Quadruple Therapy

This is the traditional quadruple regimen and involves a bismuth salt (subsalicylate 525 mg or subnitrate potassium 420 mg), metronidazole 250 mg, and

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tetracycline 375 to 500 mg, all received 4X daily, and additional to a PPI received twice per day [43]. Bismuth-based quadruple therapy is frequently employed as salvage therapy if 1st-line treatment fails, but it perhaps used as 1st-line therapy in sections of high resistance or when cost is an important consideration. A three-in-one combination capsule containing bismuth subnitrate potassium, metronidazole, and tetracycline has been developed to help reduce the pill burden, but patients still have to take three capsules four times per day additional to a PPI. The regimen is usually bestowed for ten to fourteen days. The recommended standard first-line therapy is either a bismuth-containing quadruple therapy for 14 days (PPI, a bismuth salt, tetracycline, and metronidazole) or a non-bismuth-based quadruple concomitant therapy (PPI, clarithromycin, amoxicillin, and metronidazole) for 14 days; both regimens have an extermination rate of more than 90%. **Quadruple therapy:** PPI or H_2RA once or bid + bismuth subsalicylate 525 mg qid + metronidazole 250–500 mg qid + tetracycline 500 mg qid and an alternative 1st-line eradication therapy for PCN allergic pts and often reserved as a second-line therapy after treatment failure with the PPI-based regimen. All medications except PPI should be received with meals & at bedtime for 10 days.

Levofloxacin-Based Triple Therapy

This is a 10-day regimen of a PPI and amoxicillin 1 g twice daily, and levofloxacin 500 mg once daily. It should be reserved for second-line therapy and is better tolerated than bismuth-based quadruple therapy [44]. For rescue therapy, levofloxacin-containing triple therapy (PPI, levofloxacin, and amoxicillin) achieves eradication rates of 74–81% as a second-line therapy in areas with low (10%) quinolone resistant. The chief etiology is related to the usage of NSAIDs, so discounting these managements is a vital step. In H. pylori-negative, NSAID-negative ulcers, a particularized search would be made to determine distinctive contributing factors, such as medical comorbidities, poor nutritional status, ischemia and acid hyper-secretory anomalies. The treatment of unexposed patients is depending on the classic anti-secretory therapy [45, 46]. The two classes of anti-secretory medications consummate ubiquitously used in these situations are the H_2RAs and the PPIs. Its action is by inhibition of acid production by gastric parietal cells. First medications got the outcome by obviating the histamine H_2 receptors placed on the cell basolateral membrane; they are seldom used actually and have been replaced almost completely by PPIS that acts by irreversible attaching and suppression of the H^+-K^+ ATPase pump, located on the luminal surface of the cell membrane. All PPIs achieve an identical degree of acid secretory suppression and healing rates in the management of PUD. PPIs are consummate effective when taken 30-60 minutes before meals.

Treatment for NSAID-induced ulcer: NSAIDs, involving low-dose aspirin, are the consummate significant antecedent of ulcer complications in developed countries where prevalence of H pylori infection is falling. In long-sufferings who advance uncomplicated PUD while receiving NSAIDs, greater than 90% of duodenal or gastric ulcers cure with eight weeks of standard-dose H_2-receptor antagonists (eg, ranitidine 150 mg twice a day), provided that NSAIDs are withdrawn [47, 48]. However, a current more randomized trial didn't reveal any disparate in gastric ulcer healing between groups taking esomeprazole 40 mg (85.7%), esomeprazole 20 mg (84.8%), and ranitidine (76.3%) [49]. So far, high-dose PPI has not proved better than standard-dose PPI in healing gastric ulcers in long-sufferings taking continuous NSAID therapy. **Pregnancy and lactation:** Omeprazole is categorized by the FDA as a pregnancy category C medicine, as long as entire distinctive recently present PPIs, and H_2RAs such as cimetidine and ranitidine, are category B. Although the sequences in certain analysis of prospective data have revealed that the global peril is low in pregnancy with potential toxicity during lactation, the dearth of data in humans excludes achieving definitive conclusions respecting their safety [1, 50, 51].

Stress-related erosive syndrome: 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

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effective than H_2RAs in preventing clinically important and overt upper gastrointestinal bleeding [52].

Special Circumstances in PUD older persons: Geriatric peoples are at a greater pitfall of PUD, in section because of greater-peril medicine usage, inclosing antiplatelet medications, warfarin (coumadin), SSRIs, and bisphosphonates. Compared with younger patients, older patients have less abdominal pain when they have an ulcer. Physicians should identify other risk factors for ulcers when older patients are taking NSAIDs, including previous ulcer, use of antiplatelet or anticoagulant medications, smoking, severe comorbidity or frailty, and alcohol abuse. Treatment options include discontinuing or reducing the dose of NSAIDs, choosing a less damaging NSAID or changing to a COX-2 inhibitor, or starting a PPI or misoprostol. After extermination of Helicobacter pylori, geriatric patients receiving an NSAID perhaps still necessitate maintenance PPI. However, long-term PPI use is consociated with an escalated peril of Clostridium difficile–associated diarrhea; community acquired pneumonia, interstitial nephritis, osteoporosis, and some vitamin and mineral malabsorption [53].

Children: Although GI symptoms are ubiquitous in pediatrics, PUD is rare (24.8 per 100,000 pediatric yearly). Recurrent abdominal pain is not consociated with Helicobacter pylori infection, and there is conflicting evidence respecting the association between epigastric pain and H. pylori infection. One study resulted that nausea, vomiting, and diarrhea were associated with H. pylori, but that abdominal pain and heartburn were not. Evidence based clinical guideline developed by an international panel makes recommendations for H. pylori infection in pediatric and adolescents [53].

Conclusion

H. Pylori infection or NSAID use alone may not be sufficient to cause peptic ulcer disease. Other factors like genetic and environment factors also contribute. Eradication of H. Pylori is recommended for H. Pylori-infected patients with PUD and ulcer-related complications. PPI-based triple therapy for 10 to 14 days; PPI once/bid + clarithromycin 500 mg bid + amoxicillin 1 g bid or metronidazole 500 mg bid; initial treatment of choice for eradicating H. pylori; metronidazole should be substituted for amoxicillin only in PCN-allergic individuals since metronidazole resistance is common.

Acknowledgement

The author would be grateful to anonymous reviewers by the comments that increase the quality of this manuscript.

Data Sources: Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Scopus database, Scielo and Cochrane database. Search terms included: definition, pathophysiology and management of peptic ulcer disease.

Conflict of Interest

The author has no financial or proprietary interest in any of material discussed in this article.

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