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Overview of Peptic Ulcer along with its Conventional and Improvement Therapies: A Study of Glycopyrrolate and Management of Peptic Ulcer

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Abstract: *Peptic ulcer disease remains a prevalent gastrointestinal disorder globally, posing significant challenges in its management. This comprehensive review provides an overview of peptic ulcer pathology, conventional treatment modalities, and recent advancements in therapeutic approaches. Traditional treatments, among them histamine receptor antagonists, proton pump inhibitors, and antibiotic regimens, have shown efficacy in ulcer healing and symptom alleviation. However, emerging evidence suggests limitations such as drug resistance and adverse effects. In light of these challenges, this article delves into the potential of Glycopyrrolate, a muscarinic receptor antagonist, as a novel therapeutic agent for peptic ulcer management. However, still there may be aggravation of peptic ulcer leading to severe conditions like perforated gastric ulcer, and gastric bleeding where surgery is only beneficial.*

Key Words: Peptic Ulcer , Glycopyrrolate , Ulcer Management , Helicobacter Pylori , Proton Pump Inhibitors , Histamine H2-receptor Antagonists ,Antacids, Mucosal Protective Agents

Introduction

A peptic ulcer describes an acid-peptic injury to the digestive tract that reaches the submucosa through a mucosal breach. Peptic ulcers can occur in the esophagus or Meckel's diverticulum, but they are more commonly found in the stomach (gastric ulcer) or proximal duodenum (duodenal ulcer) (Kamada, 2021). The majority of peptic ulcer disorders were previously believed to be caused by hypersecretory acidic environments, food, or stress; however, now it is believed that the infection due to H. pylori, aspirin use or other NSAIDs, and genetic factors are among the many interrelated factors that contribute to duodenal and gastric ulcers as shown in Figure 1. Although each of these factors raises the risk of ulcers on its own, the total chance of developing peptic ulcer disease is determined by the interaction of these factors with bacterial virulence factors and inflammatory responses (Silva 2011; Silva, 2011b). H. pylori infection-induced peptic ulcer development is impacted by cytokine-mediated effects on acid secretion, gastrin inhibition, and sensory neuron activation. COX-2-selective NSAIDs provide some protection against ulcer formation, but NSAIDs in general increase the risk of ulcer formation by blocking prostaglandin synthesis, blood flow, mucus secretion, and cell proliferation (Malfertheiner, 2009).

Stomach pain is by far the most prevalent sign of a peptic ulcer. Others include heartburn, nausea, bloating, or a burning sensation in the stomach as shown in Figure 1. An empty stomach and stomach acid both make the pain worse. While taking an acid-reducing medication or eating certain foods that buffer stomach acid can usually lessen the pain, the pain may eventually return. At night and in between meals, the pain could be worse. A large number of people with peptic ulcers don't even show any symptoms. Less frequently, ulcers might result in

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serious indications or symptoms like stained stools and trouble breathing. Peptic ulcers can cause internal bleeding if they are left untreated which results in anemia. Peritonitis can occur if peptic ulcers perforate—eat a hole through—the stomach or small intestinal wall (Lanas, 2017).

Figure 1

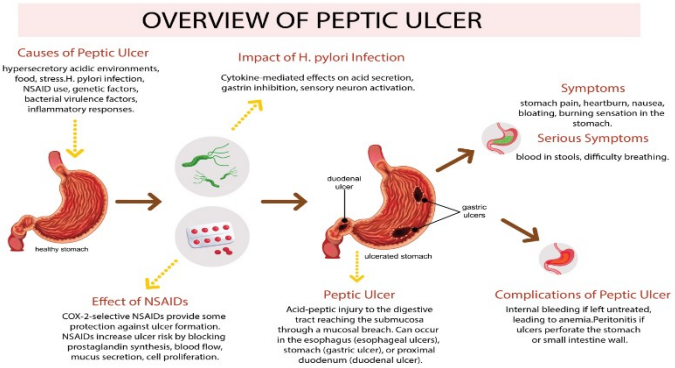

Figure 1 shows the complete overview of peptic ulcers. It mentions the definition of peptic ulcer, major potential causes, common and serious symptoms, complications, and how NSAID and H pylori impact the pathophysiology of the peptic ulcer. *Made on Illustrator*

Epidemiology

Although the frequency of peptic ulcer illness has reduced over the last several decades, there has been no change in the number of reported complications from peptic ulcer. One of the disease's severe forms is perforating peptic ulcer (PPU). A population-based retrospective study evaluated 40 years' worth of trends in PPU's incidence, presentation, and outcome.

There were 209 individuals assessed, with 113 (54%) of them being men. Out of the patients, 46 (22%) had an age above 80. Age-related increases in the incidence rate were observed. It was noted that over the study period, the percentage of people using acetylsalicylic acid increased significantly from 5% (2/38) to 18% (8/45). Throughout the 40 years of the study, comorbidity increased dramatically; in the last ten years, 22% (10/45) of the patients had an American Society of Anesthesiologists (ASA) score of 4-5, up from 5% (2/38) in the first ten years. One or more postoperative problems were experienced by thirty-nine percent (81/209) of the patients. Long-term survival and short-term death were both correlated with the ASA score. Each decade saw an increase in the median age of PPU patients. Over 50% of patients with PPU in the past ten years were older than 70. In the past ten years, women have surpassed men as the proportion of PPU patients has increased over time. Not only does H. pylori infection increase the incidence of PPU, but so do NSAID and corticosteroid use smoking, and a history of PUD. Throughout the 40-year study, comorbidity rose dramatically. Between the first and last decade, the median time from onset of symptoms to operation rose from 8 to 17 hours. 39% experienced one or more problems (Dadfar, 2020).

Helicobacter Pylori Association with Peptic Ulcer

A helical bacteria known as Helicobacter pylorus, or H. pylori, is a Gram-negative bacteria that can infect humans and cause a lifelong infection of the stomach mucosa. Helicobacter pylori (H. pylori) infection triggers an immune response in the stomach lining, leading to inflammation characterized by the infiltration of various immune cells like neutrophils, lymphocytes, plasma cells, and macrophages. This inflammatory process can cause damage to the epithelial cells lining the stomach. The inflammation in association with H. pylori infection is typically more severe in the antrum (the lower portion of the stomach) compared to the corpus (the stomach's upper part) (Narayanan, 2018).

Association of NSAIDs with Peptic Ulcer

Non-steroidal anti-inflammatory drugs, or NSAIDs, are frequently used to reduce inflammation and pain but can lead to gastrointestinal (GI) side effects. They account for the majority of ulcers, with approximately 25% of users developing peptic ulcer disease. Aspirin users are also more susceptible to developing peptic ulcers. NSAIDs can induce mucosal injury through multiple mechanisms, including entering epithelial cells and causing cellular damage, as well as inhibiting cyclooxygenase-1 (COX-1), which reduces prostaglandin synthesis necessary for maintaining mucosal integrity and blood flow (Huang, 2002]

Both COX-1 and COX-2 are inhibited by NSAIDs such as aspirin, ibuprofen, and naproxen; however, COX-2-specific NSAIDs have been linked to an increased risk of heart disease, although possibly safer for the GI tract. Patients at highest risk for NSAID-induced ulcers include those having a peptic ulcer history, concomitant use of steroids or anticoagulants, older age, and those taking high doses or multiple NSAIDs. Hence, NSAID use is linked to a high risk of gastrointestinal issues, and careful consideration of risk factors and preventative measures is essential when prescribing them (Narayanan, 2018).

H. Pylori's relationship with NSAIDs

Research indicates that the chance of developing peptic ulcer disease is increased by three to four times while using NSAIDs or if you have an H pylori infection. The findings suggest a possible interaction between NSAID usage and H pylori infection for the development of peptic ulcer disease since NSAID users with H pylori infection had a considerably greater prevalence of peptic ulcer disease compared to those without the infection. Regardless of the study design or H pylori status, it was found that one-third of patients on long-term NSAIDs experienced duodenal or stomach ulcers.

Furthermore, the use of NSAIDs increased the risk of peptic ulcers five times higher than non-NSAID use, irrespective of H pylori status. On the other hand, because of H pylori infection, the incidence of peptic ulcer disease was 18 and 3·5 times greater in NSAID users and controls, respectively. Thus, we concluded that using NSAIDs and having an H pylori infection significantly increases the chance of developing a peptic ulcer and ulcer bleeding. The co-administration of NSAIDs with H pylori infection can enhance the risk of developing peptic ulcers and ulcer bleeding (Huang, 2002).

Challenges Related to Peptic Ulcer Disease

Antibiotic Resistance

Overuse of antibiotics causes resistance to invasive microorganisms. One antibiotic is useless in treating ulcers and may even cause antibiotic resistance as shown in Figure 2. Antibiotics must therefore be used in combination. Antibiotic resistance in H pylori instances is brought on by the use of amoxicillin (AMX), metronidazole (MET), clarithromycin (CLR), tetracycline (TET), and levofloxacin (LEV) medications, which makes them ineffective (Boyanova, 2000)

Patient-Related Challenges

The main issues encountered during the treatment of peptic ulcers associated with H pylori are patient noncompliance and non-adherence. The purpose of the prescription antibiotic combination is to completely eradicate and prevent recurring peptic ulcers. However, individuals only took their prescription medication for one to two weeks at a time due to medication illness. They don't grow resistant to the antibiotics and finish their course. Treatment for the infection thus becomes challenging. (Armstrong, 1987). As shown in Figure 2.

Rapid Metabolism of Ppi

According to researchers genotyping is crucial before a patient is prescribed one.PPIs are metabolized by the P450 enzyme variant CYP2C19. Before therapy, PPI genotyping against CYP2C19 allows us to determine the optimal therapeutic dose of PPI (Cho, 2012). As shown in Figure 2.

Drug Stability in an Acid Gastric Environment

The stability of metronidazole, amoxicillin, and clarithromycin in gastric juice with omeprazole is shown in Figure 2. According to the findings, omeprazole is anticipated to improve the amoxicillin and clarithromycin's chemical stability in gastric juice. At the normal gastric pH range of 1.0–2.0, clarithromycin breaks down rapidly, however, at this pH, metronidazole and amoxicillin are sufficiently stable to maintain an antibiotic concentration in the stomach (Van, 2017).

Morphology of Bacteria and Gastric Niche

H. pylori can create biofilms, which makes it difficult to remove from the body as shown in Figure 2. Studies reveal that the gastric niche increases H. pylori defenses against severe environments and acid exposure by activating flagellar proteins and flagellin. This increases the motility of H. pylori and facilitates the bacteria's accumulation on the stomach epithelium at a higher density, which intensifies the inflammatory response (Hou, 2022).

Bacterial Load

A high bacterial density can cause an increase in inflammatory cytokine responses in the mucosa, which in turn can reduce the immune response as shown in Figure 2. The bacterial load and stomach mucosal irritation can both be decreased by H. pylori eradication (Samie, 2014).

Figure 2

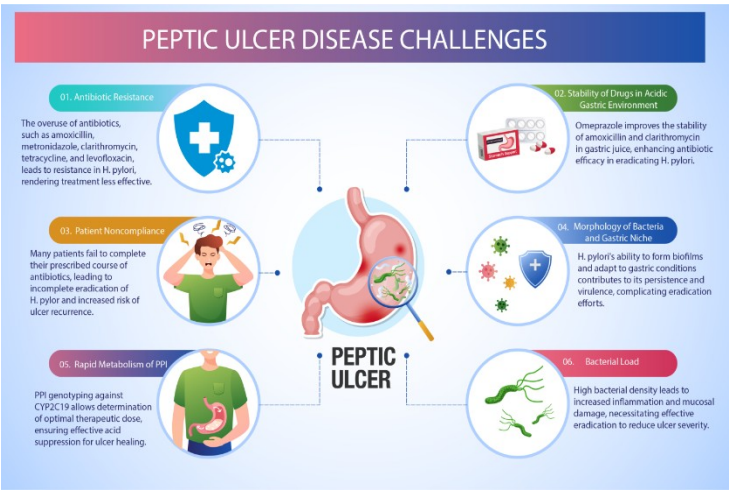

Figure 2 shows the major challenges that make peptic ulcers difficult to treat. These include overuse of antibiotics that further leads to the development of antibiotic resistance, stability of drugs in the acidic environment of the stomach, patient noncompliance, formation of biofilms, rapid metabolism of protein pump inhibitors, and bacterial load. All these challenges lead to ineffective treatment making it hard to treat peptic ulcers. *Made on Illustrator*

Treatment Strategies for Treatment of Peptic Ulcer

Conventional chemotherapies

To eradicate H. pylori, a combination of proton pump inhibitors (PPIs), H2 agonists, and medicines that limit stomach acid production is typically recommended. Three primary categories can be used to categorize the treatment.

First Line Treatment

Before developing a treatment plan for H. pylori, it is essential to obtain the patient's antibiotic usage history. A proton pump inhibitor (PPI) and two antibiotics administered over a 10-to-14-day course of treatment are the first line of treatment for H. pylori infection. First-line antibiotics consist of metronidazole, amoxicillin, and clarithromycin as mentioned in Table 1. Drug resistance, however, may result from previous exposure to clarithromycin or other macrolides. Although clarithromycin-based triple therapy was once successful, its effectiveness has decreased from 90% to 70–80%, most likely as a result of rising resistance. An alternative for treating clarithromycin resistance is bismuth-based quadruple therapy. A comparative clinical study between the two therapies showed that bismuth-based quadruple therapy had an eradication rate of 93.3%, while clarithromycin-based quadruple therapy only

achieved 69.6%. Although there are issues with bismuth availability and related complications, quadruple therapy may be beneficial (Gupta, 2023).

Second Line Treatment

Secondary therapies are taken into consideration if the first H. pylori treatment is unsuccessful. A triple treatment consisting of amoxicillin, levofloxacin, and a proton pump inhibitor (PPI) has been shown to have an 84% cure rate after ten days of treatment. Another second-line treatment option is bismuth-containing quadruple therapy, although side effects such as diarrhea, stomach pain, vomiting, nausea, and metallic taste are possible. In addition to other side effects, prolonged second-line therapy and early discontinuation can cause antibiotic resistance as mentioned in Table 1. The consensus report from Maastricht V/Florence recommends either triple or quadruple therapy with fluoroquinolones or colloidal bismuth pectin in cases where first-line clarithromycin treatment is ineffective. Rabeprazole, amoxicillin, and levofloxacin have a 94% eradication rate, whereas rabeprazole, tinidazole, and levofloxacin have a 90% elimination rate (Gupta, 2023).

Third Line Treatment

When all other treatments for H. pylori infection fail or resistance appears, rifabutin-based regimens consisting of rifabutin, Proton pump inhibitors (PPIs), amoxicillin, and levofloxacin are used as the third-line therapy. This treatment has an eradication rate of 75–90%. However, the risk of drug resistance, especially in patients with tuberculosis, and the possibility of severe, dose-dependent myelotoxicity limit the use of rifabutin.

In third-line therapy, sitafloxacin, a novel quinolone derivative, has proven to be more effective than levofloxacin against H. pylori with gyrA mutations. As an alternative to rifabutin, rifaximin is suggested because it is more readily absorbed into the bloodstream, has fewer side effects, and has superior gastrointestinal tract bioavailability as mentioned in Table 1. A Southern Italian study on levofloxacin-containing third-line treatment found that 24.37% of participants experienced adverse effects, and 1.68% of those patients experienced side effects so severe that they had to withdraw from the trial (Gupta, 2023).

Table 1

Conventional Strategies for Treatment of Peptic Ulcer

Treatment Line	Treatment Regimen	Success Rate	Considerations
First line	Triple Therapy Based on Clarithromycin	70-80%	Inspect for resistance to clarithromycin.
	Based on Bismuth, Quadruple Therapy	93.3%	Limited bismuth availability, potential complications
Second line	PPI + Levofloxacin + Amoxicillin	84%	Side effects: metallic taste, nausea, vomiting, diarrhea
	Fluoroquinolone or Bismuth-based Quadruple Therapy	90-94%	Monitor for antibiotic resistance, potential side effects
Third line	Rifabutin-based Quadruple Therapy	75-90%	Risk of drug resistance, myelotoxicity (especially in TB)
	Sitafloxacin + PPI	Variable	Effective against H. pylori with specific mutations
	Rifaximin + PPI	Variable	Improved absorption, fewer side effects, superior "Using a multi-strain probiotic compound alongside a bismuth-containing quadruple therapy can be effective in treating Helicobacter pylori infection."

Using A Multi-Strain Probiotic Compound alongside a Bismuth-Containing Quadruple

Therapy as an Effective Treatment for Helicobacter Pylori Infection

Probiotics are utilized because of their ability to modify the immune system, boost resistance to the colonization of pathogenic bacteria, and moderate and stabilize the bacterial flora of the gastrointestinal tract. It's thought that for the treatment of certain gastrointestinal disorders, a combination of probiotics containing multiple species of bacteria may work better than a single species.

Helicobacter pylori (H. pylori) infection eradication rates have declined to 70–85% due to antibiotic resistance, even though multiple treatment regimens, including double and triple therapy, have been administered. To investigate its effectiveness, a multistrain probiotic substance was added to bismuth-containing quadruple therapy for H. pylori infection in a randomized placebo-controlled triple-blind study. One hundred and sixty adult patients with peptic ulcer disease and confirmed H. pylori infection were randomly assigned to receive either a two-week probiotic compound or bismuth quadruple therapy (omeprazole, bismuth subcitrate, amoxicillin, and clarithromycin).H. pylori infection was assessed four weeks after treatment began using 13C urea breath test.

Adverse effects of therapy, patient tolerance, and dyspepsia symptoms were evaluated as secondary outcomes. This assessment uses the Short-Form Leeds Dyspepsia Questionnaire (SFLDQ), an instrument that measures three symptoms -- epigastric pain, retrosternal burning, and regurgitation - used to determine the severity of dyspepsia. The results showed that this multistrain probiotic compound had no positive effects on the rate of H. pylori eradication.

Moreover, a number of studies have been done to know the effects of combining single-strained probiotics with triple or quadruple therapy to cure H. pylori infection. In another systematic study, Sachdeva and Nagpal showed that fermented milk-based preparations (FMPs) could increase Helicobacter pylori eradication rates by roughly 5–15%.

Thus, these combination probiotics' positive effects may go beyond only their synergistic effects. There isn't any clinical data to support the idea that a combination probiotic is superior to its strains. Second, research indicates that probiotics have dose-dependently favorable effects on the elimination of H. pylori (Shavakhi, 2013).

Gastroprotectant Drugs

Treatments for peptic ulcer illness include the use of gastro-protectant medications, which may also lessen the difficulties that come with it. Gastro-protectant therapies are effective in the prevention and treatment of peptic ulcer disease and its complications, including upper gastrointestinal bleeding. A meta-analysis of over 1200 randomized trials of the major gastro-protectant drugs currently in use, involving more than 200000 participants, confirmed their efficacy in various clinical situations.

Among gastro-protectant drugs, PPIs are considered superior in the management of peptic ulcer disease, particularly in preventing, healing, and treating acute upper gastrointestinal bleeding. This superiority has been consistently observed in trials comparing PPIs with other gastro protectants of different classes, as shown in Table 2.

Regardless of whether a patient was using an NSAID (including aspirin), The benefits of gastro protectants for preventing endoscopic ulcers, symptomatic ulcers, and bleeding were significant and roughly equivalent in size. The results of this study are particularly noteworthy since they suggest that older adults who use aspirin may be at a significantly increased risk of bleeding, which could lead to greater use of gastroprotection medication (such as PPIs) in this population. It is likely that in clinical trials with patients who were classified as not using NSAIDs but had a

history of a recently healed ulcer, the absolute risk of developing endoscopic or symptomatic ulcers was higher than in trials with concurrent NSAID use. Despite conflicting evidence, we found that PPIs were more effective in preventing duodenal ulcers than stomach ulcers.

Gastro protectants lower the risk of bleeding, transfusions, and further procedures for peptic ulcer disease. Prolonged use of antithrombotic regimens in high-risk patients may allow gastro-protectant drugs, many of which are inexpensively available in generic form, to be used more widely. Potentially, by lowering the worldwide burden of peptic ulcer disease, we can also indirectly lower the incidence of cardiovascular disease (Scally, 2018).

Table 2

Gastro protectant Drugs along with Clinical Effectiveness and Key Findings

Drugs	Clinical Effectiveness	Key Findings
Prostaglandin Analogs	Beneficial in preventing and treating peptic ulcer disease.	Limited accurate studies; meta-analyses show benefits in various clinical scenarios
Histamine-2 Receptor Antagonists (H2RAs)	Beneficial in preventing and treating peptic ulcer disease.	Limited accurate studies; meta-analyses show benefits in various clinical scenarios
Proton Pump Inhibitors (PPIs)	Superior in various clinical scenarios	Superiority observed in preventing, healing, and treating acute upper gastrointestinal bleeding; significant reduction in bleeding risk; effective regardless of NSAID use More effective in preventing duodenal ulcers than stomach ulcers; concerns regarding long-term use and drug safety; potential for wider use in high-risk patients

Herbal Drugs in Treatment of Peptic Ulcer Disease

Peptic ulcer disease entails an imbalance of offensive and defensive components in the digestive tract; they are generally caused by Helicobacter pylori or excessive painkiller usage. The symptoms of peptic ulcers vary depending on the location and can range from intense, burning pain to others that are less severe. Because of their compatibility and lower side effects which are reinforced by the presence of active ingredients like flavonoids and tannins in ethno-medicinal herbs, antacids and antiulcer herbal medicines continue to command a sizable market share in the Indian pharmaceutical industry, despite advancements in synthetic drugs.

Herbs that are naturally occurring, such as valerian, demulcent, astringent, antimicrobial, and bitter herbs, can soothe, tone, address infection, promote healing, and stimulate digestive secretions to treat ulcers. Home cures include vitamin C and amino acid-rich cabbage juice and bananas, which have antibacterial properties that stop H. pylori from growing while also relieving symptoms and fortifying the stomach lining. (Anesini, 1993).

Because coconut has antimicrobial properties, it can help heal stomach ulcers. You can get relief by ingesting fresh coconut milk, gentle coconut water, and coconut oil. When included in daily routines, licorice, fenugreek, cayenne pepper, and raw honey can help treat stomach ulcers by increasing mucus production, covering the stomach lining, preventing acid secretion, and lowering inflammation (Bharati, 2012).

Garlic's antimicrobial qualities, Helicobacter pylori are inhibited, which stops stomach ulcers from developing. Mucilage from slippery elm reduces inflammation, and wood apple leaves guard against acidity in the stomach, making them natural treatments for ulcers in the mouth (Sivam, 2001).

Many herbs have antiulcer qualities, including Powdered Myrtus communis leaves help heal wounds and ulcers; a poultice made of the tender leaves of Acacia arabica acts as an astringent and stimulant; an extract from the leaves of Aegle marmelos reduces gastric ulceration; powdered Aloe vera mixed with gum acacia protects against gastric ulcers caused by indomethacin; and the bioactive compounds rich in Ficus religiosa bark and Allium sativum (garlic) juice both aid in ulcer prevention.

The tannic acid from Annona squamosa, or custard apple, has antiulcer qualities when applied as leaf paste, preventing stomach ulcers. A decoction of the roots of Beta vulgaris (beetroot) made with vinegar works well for treating a variety of ulcers, and a mixture of the powdered roots of Galega purpurea and honey is used to treat ulcers (Ranjan, 2017).

An overview of all these herbal remedies has been given in Figure 3.

Figure 3

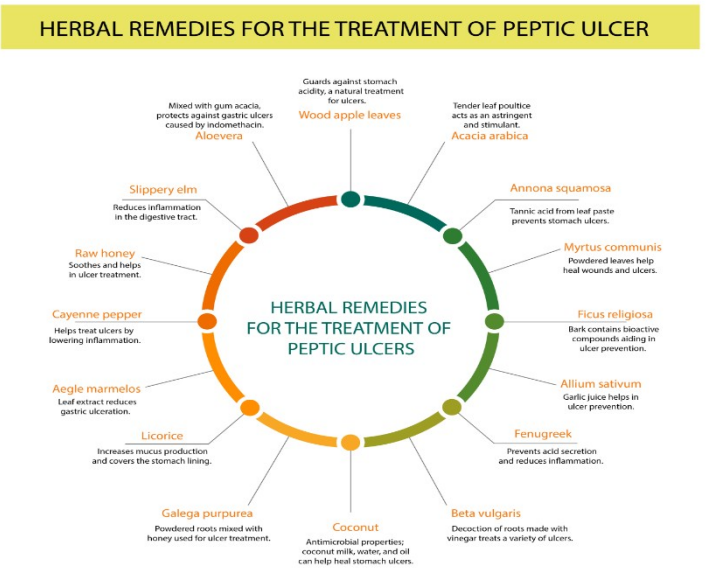

Figure 3 mentions all the herbal remedies that can be used for symptomatic relief of peptic ulcer disease

Overview of Glycopyrrolate: Understanding its Pharmacology, Clinical Effects, and Toxicology

Anticholinergic medication such as glycopyrrolate is used to decrease secretion in different parts of the body. The FDA has approved Glycopyrrolate tablets, also known as Robinul and Robinul Forte Tablets, for use in adults and children over the age of two for preoperative or intraoperative treatment. Glycopyrronium tosylate, available as cloths, was approved by the FDA in June 2018 for the topical treatment of primary axillary hyperhidrosis in adults and pediatric patients nine years of age and older. There are other medications containing glycopyrronium bromide or its derivatives that are currently in the late stages of clinical development for treating the same condition. Glycopyrronium has a strong affinity for binding to each of the five muscarinic acetylcholine (ACh) receptor subtypes and is a competitive antagonist (Penttilä, 2001).

Safety and Tolerability

Glycopyrrolate is a medication that is administered orally as a tablet. Side effects such as constipation, dry mouth, thick secretions, urine retention, and flushing were frequently reported, and more than 20% of the subjects discontinued their treatment due to these side effects (Bitsch, 1966). Inhaled glycopyrrolate has been evaluated for safety in over 4,000 participants in clinical studies and was found to not increase the risk of adverse events (Moêller, 1962). Topical glycopyrrolate (0.5%, 1%, and 2%) was also evaluated in a recent two-week trial, and one patient in the 0.5% cream cohort experienced one isolated, transient papule in the right axilla (Chabicovsky, 2019).

Comparison of Glycopyrrolate and Other Therapies

Combined therapy with LAMA and LABA has been proven to improve effectiveness while maintaining a safety profile comparable to that of each medication independently. In recent years, Botox has been approved for treating severe axillary hyperhidrosis in adult patients whose condition is not well-controlled by topical medications. However, botulinum toxin A is not a permanent cure, and patients need to receive repeat injections every six to eight months to continue benefiting from it.

Use of Novel Drug Delivery System in the Treatment of Peptic Ulcer

The treatment of peptic ulcer disease has significantly evolved over the past few years, thanks to advancements in drug delivery systems. These novel drug delivery systems have revolutionized the way medications are administered to effectively target and treat peptic ulcers (Hamedeyazdan, 2024). By utilizing polymeric and magnetic nanoparticles, as well as covalently or non-covalently attached drugs, drug delivery systems can specifically deliver medications to the target site. These systems have demonstrated promising outcomes in the treatment of peptic ulcers, ensuring enhanced performance for both therapeutic and diagnostic applications as mentioned in Table 3.

Table 3

Novel drug delivery systems along with drugs and their potential benefits

Novel Drug Delivery System	Drug(s)	Benefits
Floating microspheres	Clarithromycin, Lisinopril	Improved drug entrapment, delayed release, prolonged stomach retention.
Floating beads	Amoxicillin trihydrate	pH-sensitive, extended stomach retention, enhanced H. pylori eradication, improved absorption.
Floating pellets	Amoxicillin trihydrate	High drug release (97% in 24 hours).
Floating tablet	Clarithromycin, Amoxicillin trihydrate, Metronidazole, Levofloxacin	Regulated, extended-release, specific dosing, localized activity.
Floating in-situ gel	Metronidazole	Reduced dosage, sustained release, effective H. pylori eradication.
Gastro retentive nanofibrous film	5-fluorouracil	Enhanced chemotherapy, potential targeted therapy for stomach cancer.
Gastro retentive wafer	Levofloxacin hydrochloride	Prolonged activity against H. pylori.
Mucoadhesive microspheres	Famotidine	Enhanced drug release, localized action.
Gold NPs	Fruit extract of Tribulus Terrestris	Efficacy against H. pylori.
Zinc oxide (ZnO) NPs	Metronidazole	Disruption of bacterial cell membranes, induction of bacterial death.
Silver NP	Aqueous extract of Toxicodendron vernicifuum	Antibacterial efficacy against H. pylori.
Bismuth NPs	Bismuth	Suppression of H. pylori growth by affecting bacterial metabolism.
PLGA Nps	Clarithromycin	Effective against clinical H. pylori strains.
Polymeric NPs	Amoxicillin	Effective treatment of H. pylori with controlled release.
Lipid-based NPs	Clarithromycin	Treatment of H. pylori infection by clearing mucous layers and biofilm.

Surgical Approach for Peptic Ulcer Disease

Surgical Approach for Recurrent Peptic Ulcer

Recurrent peptic ulcers can pose a challenge in terms of management, requiring surgical intervention in some cases. Surgical management of recurrent peptic ulcers may involve various procedures such as gastric resection or gastrectomy with vagotomy. These procedures aim to remove the source of acid production or alter the anatomy of the stomach to reduce acid secretion. Additionally, the use of PPIs and histamine2-receptor antagonists may be utilized to further suppress gastric acid production and promote healing. It is important for patients with recurrent peptic ulcers to also make lifestyle modifications, such as reducing alcohol consumption and avoiding the use of antihistaminic receptors (Stewart, 2008).

In some medical centers, the decrease in elective surgeries for peptic ulcer disease has been reversed through the adoption of laparoscopic techniques for treating duodenal ulcers. This decline had been attributed to the widespread use of potent gastric acid-suppressive drugs. A multicenter study was conducted on 136 patients to investigate the outcomes of laparoscopic posterior vagotomy and anterior linear gastrectomy. The study aimed to sever gastric vagus branches. Although the term "anterior linear gastrectomy" may be misleading, it essentially involves cutting and stapling along the lesser curvature of the stomach using an endo-stapling device. The procedure showed promising results with an average operating time of 65 minutes, zero mortality, 3% perioperative morbidity, and an average hospital stay of 3 days. Gastric acid secretion decreased by approximately 80%, with only one patient experiencing an asymptomatic ulcer recurrence during a 2-year follow-up. However, four patients reported reduced quality of life according to the Visick score. While the procedure appears relatively straightforward, the lack of clearly defined surgical indications and the absence of data regarding H. pylori infection pose limitations. Laparoscopic surgery to reduce gastric acid secretion may present an alternative for the 10-20% of patients in whom H. pylori eradication fails and in cases of recurrent peptic ulcers despite eradication (Gómez, 1996).

Laparoscopic surgery for the management of peptic ulcers and reduction in gastric acid secretion is still in use in 2024. This approach remains a part of the modern surgical armamentarium for treating peptic ulcer disease, especially when medical therapy is insufficient or when complications arise. Advances in laparoscopic techniques and instruments, as well as in perioperative care, continue to improve the safety, efficacy, and recovery times associated with these procedures. Moreover, despite the prevalence of effective medical treatments, such as proton pump inhibitors and H2-receptor antagonists, surgery may still be indicated for cases with complications like bleeding, perforation, or obstruction, and in patients with recurrent ulcers refractory to medical therapy. As such, laparoscopic surgeries including vagotomy, partial gastrectomy, and anti-reflux procedures are still relevant and practiced in 2024, with ongoing research and development likely continuing to refine these techniques further (Chi, 2022; Latif, 2022).

Surgical Approach for Complicated Peptic Ulcer

Surgery is no longer the first-line treatment for peptic ulcer disease. It is now mainly used to manage complications that arise from the disease. About two-thirds of the surgeries performed are meant to address perforations leading to peritonitis. The remaining one-third is performed to control bleeding from peptic ulcers, even though endoscopic treatments are available. In rare cases of peptic ulcer penetration, surgery may be required. Additionally, 1-2% of patients with peptic ulcer disease may undergo surgery for gastric outlet obstruction. This usually results from recurrent ulcers near the pylorus, leading to scarring and narrowing. Overall, surgical intervention for peptic ulcer disease is primarily focused on treating emergent complications such as perforation, bleeding, and obstruction (Hermansson, 1997).

Surgical Approach for Perforated Peptic Ulcer Disease

A range of surgical techniques has been explored that can prove beneficial in treating peptic ulcers. Studies found laparoscopic repair to be comparable to open surgery, with a lower risk of wound infection. (Birol, 2019) Searchers reported successful endoscopic closure in a challenging case, while several other studies highlighted the safety and efficacy of laparoscopic repair, with the latter suggesting it as the primary approach (Bechara, 2018). These studies collectively suggest that laparoscopic techniques, including primary repair and endoscopic closure, may offer favorable outcomes in the management of perforated peptic ulcer disease through surgical techniques (Kostov, 2019; Manco, 2020).

Conservative treatment may be suitable for around two-thirds of patients with peptic ulcer perforation. However, delaying surgical intervention beyond 12 hours from the onset of clinical symptoms can significantly worsen the outcomes for patients. Therefore, it is critical to promptly recognize indications for surgery and avoid delaying a laparotomy when it is necessary. Early surgical intervention is crucial to improve outcomes in cases of peptic ulcer perforation (Zittel, 2000).

Surgical Approach for Peptic Ulcer Bleeding

Advances in the surgical management of peptic ulcer bleeding have focused on reducing rebreeding rates and improving primary endoscopic hemostasis (Chiu, 2019). Endoscopic hemostasis, which includes injection, thermal therapy, and mechanical therapy, has proven to be effective. However, newer modalities like over-the-scope clips, topical

hemostatic sprays, and endoscopic ultrasonography-guided angiotherapy have been developed to address difficult cases (Jang, 2016). For patients who do not respond to initial endoscopic treatment, direct surgical control of the bleeding, with or without additional acid-suppressing procedures, may be necessary (Ezekian, 2016). Nevertheless, the safety and efficacy of these techniques, including endoscopic radiofrequency energy exposure, require further investigation.

Surgical Approach for Gastric Outlet Obstruction

Gastric outlet obstruction is relatively rare, with approximately 1–3 cases per 100,000 inhabitants per year in Finland. Around 1–2% of peptic ulcer patients develop this complication, predominantly caused by duodenal ulcers. Symptoms include vomiting and weight loss due to restricted fluid and caloric intake. Endoscopy or gastroduodenogram reveals pyloric narrowing, requiring exclusion of malignancy via biopsy, as malignant tumors are a common cause of obstruction. Conservative management with nasogastric decompression and intravenous hydration may be successful in acute cases, while chronic obstruction may necessitate endoscopic or surgical intervention.

Endoscopic balloon dilatation is attempted initially, with short-term success rates ranging from 83–100%. However, long-term outcomes are often unsatisfactory, with 30% of patients eventually requiring surgery due to recurrence or persistent symptoms. Surgical options include gastric resection with vagotomy or gastrojejunostomy, with pyloroplasty often not feasible due to scarring. H. pylori infection is common in patients with gastric outlet obstruction, and eradication is recommended, although its impact on outcomes remains uncertain.

Surgery for peptic ulcer disease causing gastric outlet obstruction should have less than 15% and 5% morbidity and mortality rates respectively. Antrectomy/Billroth-I resection may lead to 5-8% re-stenosis. Proximal selective vagotomy is not recommended due to high recurrence rates. Patients with obstruction and H. pylori infection who underwent balloon dilatation and eradication had lower subsequent surgery rates. Gastric outlet obstruction management requires endoscopic intervention followed by surgery if necessary, considering the patient's overall clinical condition and response to treatment (Zittel, 2000).

Conclusion

This review concludes by outlining how the management of peptic ulcers is changing and stressing the ongoing search for better treatment approaches. The complexity of peptic ulcers, which include elements like acid secretion, H. pylori infection, and mucosal integrity, emphasizes the value of a thorough and individualized approach to patient care.

With its capacity to control stomach acid secretion and lessen the side effects of conventional treatments, glycopyrrolate's role as a promising adjunct in the treatment of peptic ulcers emerges in this context. Glycopyrrolate incorporation into treatment plans is a step in the right direction toward maximizing effectiveness and reducing side effects, which will improve the patient experience in the long run.

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