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Current Therapeutic Approaches in Acid Peptic Disease

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Abstract

Around 8 million people die every year from gastric and hepatic problems. Worldwide peptic ulcers are 8.4% of the population. Stomach cancers, reflux disease, and helicobacter pylori infection are some of the causes. The acid peptic disease is caused by excessive amounts of acid produced. There are three phenotypes of gastroesophageal reflux disease which are mucosal injury which is reflux, related to endoscopic evidence, where the inner lining of the esophagus is abnormal, Barrett's esophagus, and where there is no esophageal mucosal injury on the endoscopy is non-erosive reflux disease. Heartburn and regurgitation, pain in the abdominal area, and disturbance in sleep pattern are signs of typical reflux syndrome. Endoscopy-negative reflux disease and non-erosive reflux disease are based entirely on endoscopy. While the brain and gut are communicating continuously, a few like the hypothalamic-pituitary-adrenal axis are known to be associated with the modulation of the gut-brain axis. Drugs like antacids, omeprazole, rebamipide, revaprazan, and many new drugs are being studied. Policymakers have to keep this in mind as this condition is only increasing in the coming years with newer technology like artificial intelligence and a prophylactic vaccine could be the best or better alternative. Let us hope for better treatment options both non-invasive and invasive in the coming years with helicobacter infection being the main contender and with newer technology like artificial intelligence, let's hope for better and improved drugs with negligible or very fewer adverse effects.

Keywords: Gastritis • Gastroesophageal reflux disease • Non-erosive reflux disease • Erosive reflux disease • Proton pump inhibitors • Potassium-competitive acid blockers

Introduction

The peptic acid disorder causes reflux disease is caused by anti-inflammatory drugs, cigarette use, stress, and infection caused by *H. pylori*. A large number of the cases may predispose to gastric carcinoma, where gastritis seen is related to H. pylori. Abdominal pain is the symptom that appears initially. Drugs are cytoprotective and help eradicate *H. pylori* infection [1]. Peptic ulcers can lead to fatalities if not treated on time and the prevalence in the world is around 8.4% between 17-82 years (Figure 1). The gut is in a form of an alphabet J, consisting of different layers. The neck cells secrete mucus; hydrochloric acid is secreted by the parietal cells with the G cells secreting the hormone gastrin. Gastroesophageal Reflux Disease (GERD) causes discomfort due to backflow from the gut that connects the throat and gut is experienced by a feeling of burning and regurgitation and reflux esophagitis is preferred over erosive esophagitis [2].

Heartburn and/or regurgitation, pain in the abdominal area, and disturbance in sleep pattern are signs of typical reflux syndrome and when the absence of esophageal injury it is an example of typical reflux syndrome, while if associated with esophageal injury is reflux esophagitis. A typical feature of GERD is Endoscopy Negative Reflux Disease (ENRD) while the uncomplicated type is Non Erosive Reflux Disease (NERD). GERD is manifested by esophageal and extraesophageal syndromes the major symptom of GERD being epigastric pain, centered in the upper abdomen Despite daily treatment with PPIs symptoms persist in 20%–30% of GERD patients [3].

Three phenotypes in GERD are due to mucosal injury which is reflux, where the esophagus inner lining is abnormal, Barrett's esophagus, and in Non Erosive Reflux Disease (NERD) there is the absence of mucosal injury on endoscopy of the esophagus. This is based on unusual exposure to acid in the esophagus and pH testing. Gastroesophageal sphincter pressure is minimal in NERD patients. Hiatal Hernia (HH) and esophageal exposure during nighttime are minimal when compared to those with reflux esophagitis. A clinical feature seen in GERD is NERD and EE (Figure 2) with asthma, cough, hoarseness, and chest pain in some patients. Patients have no signs of esophagitis in about 30% to 70% of patients but based on endoscopy, complaints have been noted.

Norman Barrett, an Australian surgeon, described chronic GERD that damages the esophagus inner lining of the esophagus and is diagnosed by endoscopy after which Barrett's esophagus is named, which is seen in the short segment (Figure 3). Another way of identification is the criteria, Prague C and M, where C is the circumferential and M is the maximum extent of Barrett's metaplasia [4].

The severity of reflux disease is graded A, B, C, and D depending on the break in the mucosa and this is supported by the Gastroenterology organization. The disadvantage is that the mucosal changes are excluded, and with advances in endoscopy, these disadvantages can be rectified.

The staging of gastritis was classified depending on the biopsy score obtained and through biopsy for gastric absence; 0, 1, 2, and 3 scored the mucosal atrophy. A VAS with a score of 0, 1, 2, and 3 was used for inflammation in the mucosa that was used as a reference for each biopsy site and the overall score combined with the scores for gastritis were obtained from a biopsy.

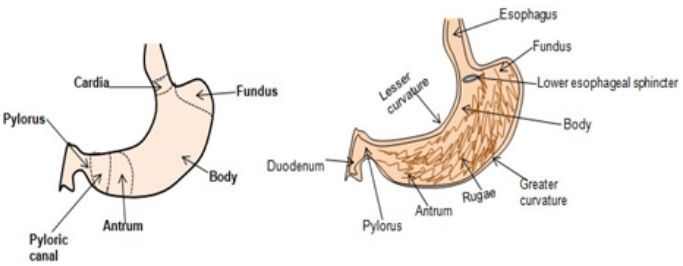

Figure 1. Stomach and its region.

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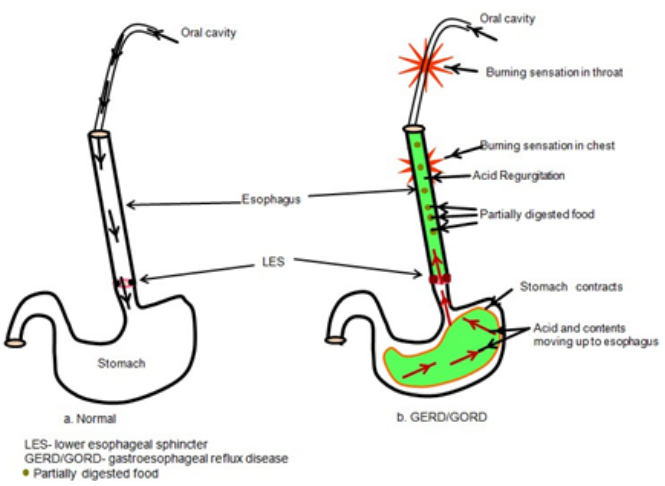

Figure 2. GERD process.

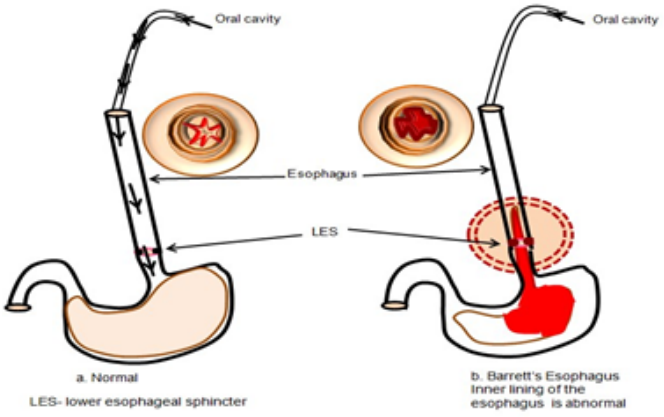

Figure 3. Barrett's esophagus.

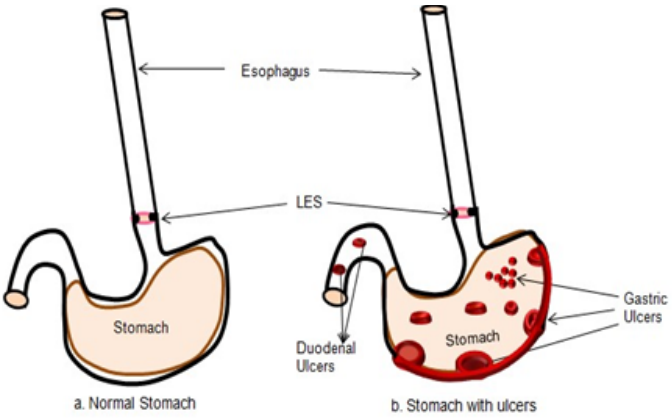

Figure 4. Sites of ulcers.

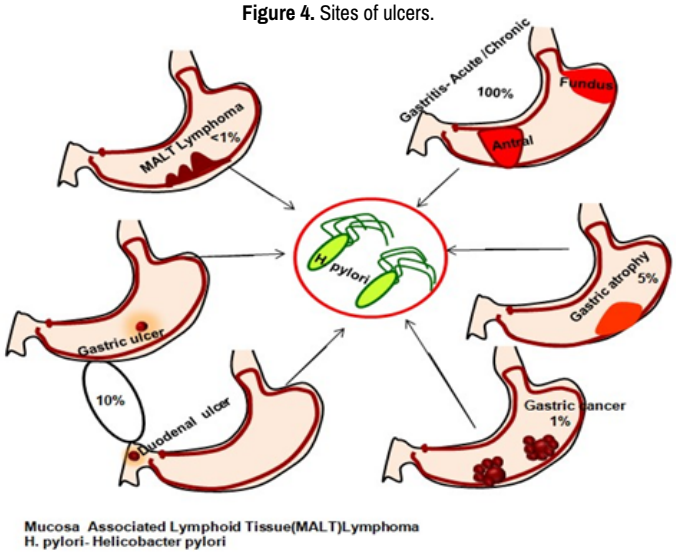

Figure 5. *H. pylori*-associated conditions.

Literature Review

The little brain

The little brain, referred to as the second brain, has a lining from the esophagus to the rectum, is modulated by the Hypothalamus-Pituitary-Adrenal Axis (HPA), to name a few and stress is also a known factor to alter the commensal microbiota and continuous communication occurs between brain and gut and their correlation is well known. Bacteria, fungi, and viruses, comprise the commensal microbiota, with food being a factor. The commensal microbiota is different in the stomach with GBA being a key player. Drugs like omeprazole, rabeprazole, and ranitidine, are frequently prescribed, with antacids, baclofen, alginate, and prokinetics as an add-on with drugs, intervention, and surgery being some of them. With proton pump achievements, some lacunae remain to be resolved in certain areas, especially in the control of acid secretion [5].

Peptic ulcer disease

The upper gut complications include gastritis, erosions, including ulcers. The ulcers are large and extend deeper into the mucosa. The antrum is the primary site associated with bleeding, strictures, and perforations. Among NSAID users, ulcer-related complications are higher, compared to non-users, and classified according to the cause of mucosal damage. (Figure 4) Some sources of bleeding in peptic ulcers are related to epigastric discomfort, frequent use of aspirin or other NSAID use and PUD history have been associated with *H. pylori* infection [6]. Peptic ulcers are usually associated with *H. pylori*; drugs like aspirin, ibuprofen, and mucosal damage due to stress while the idiopathic causes are due to non-*H. pylori*, non – NSAID, Zollinger- Ellison syndrome (ZE syndrome), Crohn's disease, and chronic peptic ulceration, linked to conditions like cirrhosis, Chronic Renal Failure(CRF), heart-related problems, and idiopathic peptic ulcers [7]. The pathophysiology of ulcer depend on the balance between gastric content and inactive form of pepsinogen (Figure 5).

The parietal cells secrete gastric acid and the chief cells, release pepsinogen. Pepsin is activated by acid pH, which in turn facilitates the endogenous Prostaglandins (PGs) activating pepsin mucosal integrity and repair. *H. pylori* or NSAIDs play a role in peptic ulcers.

The proton pump

The hydrogen ions for H^+K^+ ATPase are secreted and found only on the secretory membranes of parietal cells. Stimulation of tubulovesicles helps migration, where the H^+K^+ ATPase secrete protons directly into the lumen.

Acid peptic disease and its treatment approach

Antacids: The mechanism is by neutralizing acid, thus pepsin is inhibited by antacids on empty stomach it takes a lesser time but is increased when administered with food. Antacids containing hydroxide of aluminium magnesium and calcium carbonate. For the rapid and early effects of symptoms, antacids are used. Insoluble antacids are commonly used. Constipation is caused by aluminium and calcium-containing products while diarrhea is seen by magnesium-containing products, hence combined. Diarrhea can occur if magnesium-containing antacids are administered as monotherapy in renal insufficiency patients, causing hypomagnesaemia. Aluminium-containing antacids are known to cause encephalology and osteomalacia. H2RAs like ranitidine, and drugs like omeprazole, rabeprazole have largely replaced antacids and with H2-receptor antagonists.

Histamine -2 receptor antagonists (H2 receptor antagonists): It was described way back in 1972. The treatment of PUD was revolutionized by cimetidine, ranitidine, famotidine, and nizatidine. When administered once a day at bedtime, it reduces acid secretion at night time [8]. H2-receptor antagonists are known to prevent ulcers associated with low-dose aspirin rather than NSAIDs.

Proton Pump Inhibitors (PPI): PPIs available are rabeprazole, dexlansoprazole, dexlansoprazole, and other compounds. PPIs are prodrugs that inhibit the H^+K^+ ATPase and are found to be more effective than H2 antagonists. They act by converting into active sulfenamide, increasing the period of action

and blocking the mechanism independent of histamine, acetylcholine, or gastrin stimulus for acid secretion and for ulcers, it has become a game changer. It is found that rates of 2–6% of Caucasian and a higher percentage of healing in helicobacter infection are seen in 15–20% and Asian populations. The safety profiles of all PPIs are excellent. Hypergastrinemia, gastric atrophy, and chronic hypochlorhydria are the main concerns regarding PPIs.

Potassium-competitive acid blockers (P-cabs): Food stimulates secretion from gastric glands, although it can also occur due to the stimulation of H2 receptors, M3 receptors, and CCK2 receptors. For acid suppression, several P-CABs have been developed. These have rapid response, with a longer or increased time thus having, and very strong blocking effect of acid in comparison to inhibitors of proton pump [9].

Discussion

Mechanism of action

P-CABs bind in such a way that they can be removed from the site even with an increase in the concentration of the drug site and revert. This leads to quick transfer of the proton and gets collected at an excessive concentration in the channel or duct. In the intestine, the undigested food helps in stimulation leading to a reduction in the formation of acid, these drugs bind to both forms resulting in the anti-secretory effect that is quick and better (Figure 6).

The first P-CAB was an anti-secretory drug SCH28080, which inhibited the proton pump competitively but stopped due to severe hepatotoxicity. AZD0865 was another drug developed that was potent, that had fast action. The first P-CAB revaprazan showed no advantage over PPIs. Vonoprazan fumarate which was marketed in Japan displayed some advantages over PPIs.

Revaprazan (YH1885): It was approved in 2007for gastritis and ulcers. It has been observed that the healing effect of the gut decreases the signaling of MAPK ERK1/2 displaying anti-inflammatory properties. Revaprazan displays a significant anti-inflammatory property and after helicobacter infection develops, the signal gets inactivated for Akt, NF-κB, and cytokines.

Vonoprazan fumarate (TAK-438): It was approved in 2015 and had early onset, long duration, and potency greater than PPIs. It is used to treat stomach ulcers, heal and prevent erosive esophagitis, protect the gut, especially in those taking aspirin, and eliminate *H. pylori* infection.

Tegoprazan (CJ-12420, K-CAB): This drug is indicated in reflux disease, which is a benzimidazole derivative and Phase III migratory motor complex (MMC) is induced by this drug. This drug could also be an alternative for patients with motility impairment [10].

Linaprazan (AZD0865): Linaprazan in animal studies and studies on patients, this drug displayed rapid and long acid secretion reduction which is dose-dependent having an effect at a lower dose than omeprazole. In Europe, a new formulation, (that is a prodrug) is under investigation. This is used as an add-on in whom PPIs are resistant and known to display significant effects.

Fexuprazan (DWP14012): This compound is being developed. The suppression is dependent on the dose. Acid production is suppressed, similar to or to a more than vonoprazan displaying a quick and long-standing suppression of secretion of acid and no hepatotoxicity being an advantage in human studies.

Kpf-h008: In preclinical studies, this compound was found to be very effective compared to PPI like lansoprazole concerning its blocking /inhibitory action.

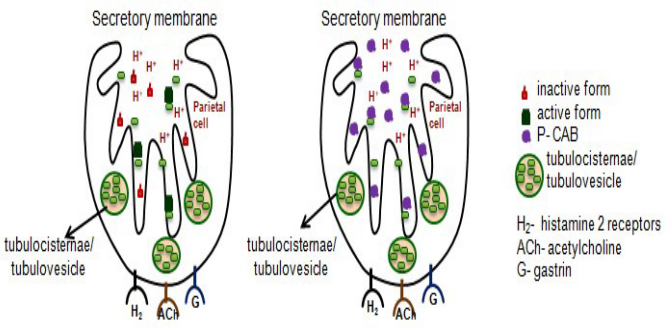

Figure 6. PPI and P- CAB – how do they work?.

Mucosal protecting drugs

Rebamipide: The mucosal protection is rebamipide a quinolinone. In South-East Asia, for esophageal acid-related disorders, and is available Over The Counter (OTC). The increase in the synthesis of Prostaglandins (PG) leads to improvement where the Prostaglandin EP4 genes (PGEP4) along with Epidermal Growth Factor (EGF) are induced, activating gut mucosa.

Hyaluronic acid and chondroitin sulfate: This mixture of poloxamer 407 is indicated against gastric refluxate, which serves as a protective barrier. Improving GERD-related symptoms, gastritis pain, and discomfort was observed at 52.6% versus 32.1%, with combination with PPI than with placebo and PPI.

Bismuth: The US FDA approved the combination with other agents for the elimination of helicobacter pylori infection. It has modest efficacy in non-ulcer dyspepsia, promoting the ulcer to heal where the pepsin is inhibited. Secretions are increased of mucosal, mucus, and bicarbonate secretion. It forms bismuth sulfide in the colon with the formation of black stools, due to a reaction with hydrogen sulfide. It is unabsorbed, eliminated in stool, and is recommended in helicobacter pylori regimens.

Misoprostol: This drug is recommended in NSAID- induced ulcer prevention and indicated in NSAID- induced ulcers. Misoprostol in low doses is indicated and administered daily in case of NSAID- induced ulcers with less adverse effects, and preventing ulcer complications has been suggested through endoscopic studies.

Cox-2 inhibitors: These drugs offer hope for minimizing the gut toxicity of NSAIDs like aspirin, at the same time helps in maintaining the effectiveness in combination with PPI in ulcer. Although they have improved gastric safety, they are associated with cardiovascular risk and bleeding.

Gastroesophageal reflux disease- Future drug

Some of the drugs excepted in near future are 'Transient Lower Esophageal Sphincter Relaxation' (TLESR) reducers. Some of the triggering agents known are Gamma-Aminobutyric Acid B (GABAB), metabotropic Glutamate Receptor 5(mGluR5), Cannabinoid 1 (CB1), Muscarinic Cholecystokinin (CCK), 5-Hydroxytryptamine 4 (5-HT4), and opioid receptors. Presently the development of TLESR has been stopped and may be reconsidered in the future.

Prokinetics: In GERD, prokinetics appear to have some moderate to best clinical benefits, but several adverse effects avoid its use. In patients who are intolerant to omeprazole, rabeprazole is considered a first-line drug. Several clinical trials conducted have shown or observed that combination therapy of PPI with prokinetic agents would be quite effective with a Quality of Life (QoL) improvement, rather than when PPI has been administrated alone.

Acotiamide (Acofide, YM-443 and Z-338): This drug inhibits the breakdown of acetylcholine from nerve terminals in a selective manner and is currently approved in Japan for patients who are experiencing it for a long time and who do not have ulcers.

Prucalopride: This is a 5-HT4 agonist that is prescribed for constipation, especially the chronic type. Different studies reveal that this drug displayed evidence for acid suppression. In patients, activity is enhanced in whom there is an exposure of acid to the esophagus and thus motility is increased. This compound is a first in this type.

Pumosertag (DDP733): This compound is a 5-HT3 agonist. Evidence in animal studies reveals that this compound helps to increase the gastroesophageal sphincter pressure with a significant reduction in the contractions of the esophagus without affecting the basal pressure in trials [11].

Pain modulators

A valuable suggestion is the use of neuromodulators in acid disorders and the drugs like rabeprazole, and dexlansoprazole in such patients are appreciated thus demonstrating their role in functional disorders in whom PPIs did not work.

Prostaglandin E2 (PGE2) receptor: PGE2 formed during inflammation is prevented by the action through the antagonistic effect on the receptor EP1, which is precise for chemical-induced ulcers. Phase 1 study that has been revealed or yet to be published, an antagonist of EP1 was tried in healthy non-erosive reflux disease.

Surgery therapy: The only indications for surgery are patients with uncontrolled bleeding during the endoscopy procedure. A few surgical options

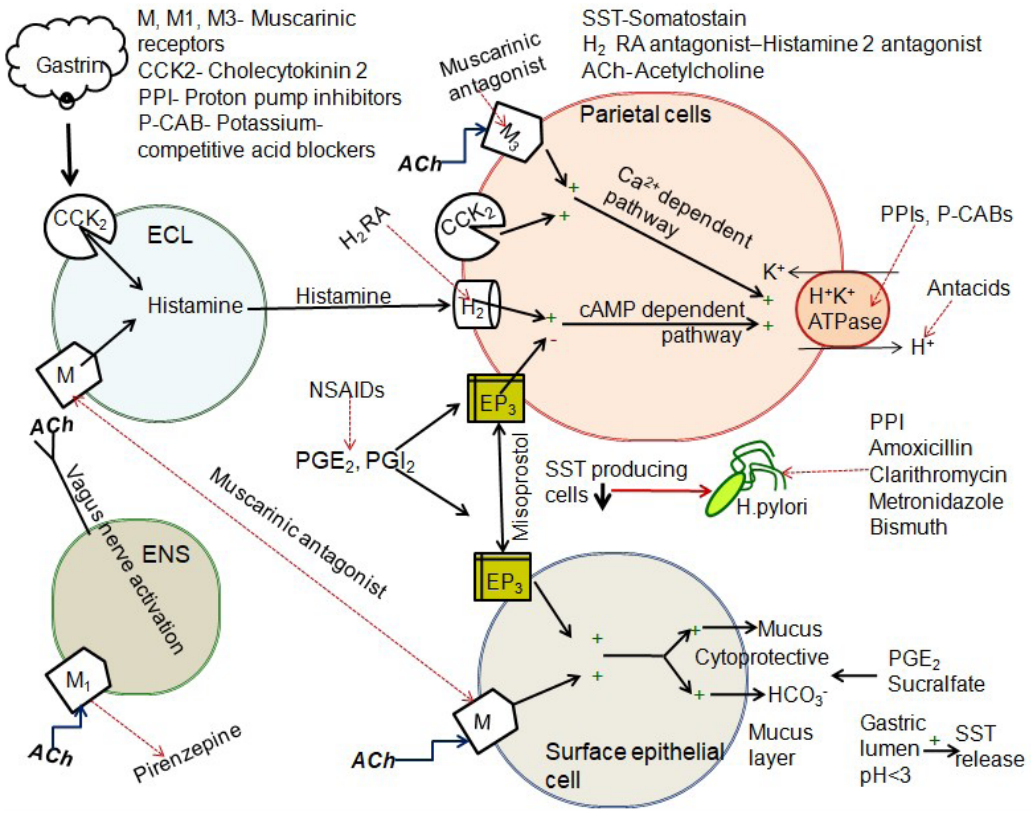

Figure 7. Acid peptic disease and its treatment approach.

Table 1. Summary of some of the drugs in acid peptic disease and their mechanism.

Drug	Mechanism
Antacids	Neutralise acid
H_2 receptor antagonists	Inhibits H_2 receptors
Proton Pump Inhibitors (PPI)	Inhibit H^+K^+ATPase
Potassium-Competitive Acid Blockers (P-CABs)	Bind reversibly to K^+ ion and inhibit H^+K^+ATPase
Rebamipide	Prostaglandin generation is stimulated in gastric mucosa
Hyaluronic acid and chondroitin sulfate	Mucosal protecting agent
Bismuth	Acts as a diffusion barrier for HCl
Misoprostol	Inhibits basal and nocturnal gastric acid, through stimulation of prostaglandin E1(PGE_1)
Acotiamide	Inhibits the breakdown of acetylcholine from nerve terminals

for such patients include pyloroplasty, subtotal gastrectomy, patch repair for ulcer perforation, and oversewing of bleeding vessels to name a few [12].

Summary of the drugs used in acid peptic disease and its treatment approach (Figure 7). As we come to towards the end of the review, here is a summary of the acid peptic disease drugs and their mechanisms is given below (Table 1).

Conclusion

Two very promising alternative clinical trials are underway, that is not known to affect the mucosa of the gut but have an anti-inflammatory effect as well. With newer drugs being developed for the acid peptic disease we can expect better treatment in the coming year's number of drugs are under trial. Vaccines for acid disorders are being developed as they would be a boon for patients due to the need. A prophylactic vaccine could be the best or better alternative. Policymakers have to keep this in mind as this condition is only increasing in the coming years. Let us all hope for better treatment options both non-invasive and invasive in the coming years with helicobacter infection being the main contender.

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Author Contribution

All the authors, P. Vinod Kumar, Princy Louis Palatty, and Achuthan CR were involved in all aspects of this manuscript, from conceptualization, writing, and editing and all figures in the manuscript have been created by the author.

P. Vinod Kumar - Conception, Design, Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review, Writing.

Achuthan CR- Conception, Design, Supervision, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review, Writing, Critical Review.

Princy Louis Palatty- Conception, Design, Supervision, Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review, Writing, Critical Review.

Conflict of Interest

Authors declare no conflict of interest

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