# Peptic Ulcer Disease: Descriptive Epidemiology, Risk Factors, Management and Prevention

**Aejaz Habeeb, Santosh K Tiwari, Avinash Bardia, Shaswathi Khan, Sandeep Kumar Vishwakarma, Safwaan Habeeb and Aleem Ahmed Khan***

Central Laboratory for Stem Cell Research & Translational Medicine, Deccan College of Medical Sciences, India

***Corresponding author:** Aleem Ahmed Khan, Scientist, Central Laboratory for Stem Cell Research & Translational Medicine, CLRD, Deccan College of Medical Sciences, Kanchanbagh, Hyderabad 500 058, Andhra Pradesh, India. Tel: +91-40-24342954; Email: aleem_a_khan@rediffmail.com

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## BACKGROUND

Peptic ulcer is a break (like a sore) in the lining of the stomach or the upper part of the small intestine [1], with a diameter of at least 0.5 cm penetrating through the muscularis mucosa. It is typically a non-fatal disease that majorly represented by symptoms of epigastric pain typically relieved by food or alkali, often exhibit periodicity. Peptic ulcers or PUDs are generally categorized based on their anatomical origin as gastric or duodenal. Gastric ulcers are found along the lesser curvature of the stomach, and duodenal ulcers usually occur in the duodenal bulb, the area most exposed to gastric acid [2]. Helicobacter pylori had been thought as the main etiological factor for 90% duodenal and 80% gastric ulcers [3]. With recent decline in prevalence in *H. pylori* in western countries, PUDs, especially gastric ulcers Nonsteroidal Anti-Inflammatory Drugs **(NSAIDs)** and Acetylsalicyclic Acid **(ASA)** [4-5]. In this part of the world, the incidence of duodenal ulcers is approximately four-fold higher than gastric ulcers; constratingly elsewhere, gastric ulcers are more common. Gastric ulcers predominantly arise in subjects over 40 years old whereas,

duodenal ulcers in particular occur between the ages of 20-50 years [6]. Improved management and adaptation of hygienic conditions led to decrease in prevalence of PUDs, the widespread use of NSAIDs and low-dose ASA still keep burden of PUDs a concern. National estimates of various countries have shown direct medical costs associated with PUDs were USD163-866 per patient [6].

**Keywords:** Peptic Ulcer; H pylori; Gastrointestinal Diseases; Treatment

# EPIDEMIOLOGY

Epidemiological shows that PUD remains a relatively common condition worldwide, with annual incidence ranging from 0.10% to 0.19% for physician-diagnosed PUD and from 0.03% to 0.17% for PUD diagnosed during hospitalization [7]. The 1-year prevalence of physician diagnosed PUD was 0.12–1.5%, and the 1-year prevalence of PUD diagnosed during hospitalizations was 0.10–0.19% [7]. The data show that the incidence of PUD has decreased over recent decades in many countries, most likely as a result of the decrease in *H. pylori* infection, particularly in Western populations. However, it is possible that the situation may be different in Asian countries; a recent study in Korea revealed that the prevalence of *H. pylori* infection in association with GU was increasing with time, whereas *H. pylori* infection in DU was decreasing [8]. The most reliable study of physician-diagnosed prevalence was from Sweden, reporting cross-sectional data representative of the general population [9]; the study thus included both symptomatic and asymptomatic PUD. The overall prevalence of PUD observed in this study was 4.1%; 19.5% of all PUD cases identified were asymptomatic. Comparing this prevalence with the lower rates obtained from other studies of physician diagnosed PUD in primary care suggests that a proportion of individuals with PUD remain undiagnosed. In individuals with asymptomatic PUD, severe complications, such as gastrointestinal haemorrhage, may be the first signs of the disease. Haemorrhage is associated with mortality approaching 10% and high recurrence [10]. Literature shows that the reported incidence and prevalence of PUD have decreased over time in recent decades. However, temporal trends in the rate of hospitalizations for complications of PUD varied, remaining unchanged or increasing in recent decades in two studies in Finland and the Netherlands [11-12], but declining over time in one study in Scotland [13]. The lifetime risk for peptic ulcer in infected individuals ranges from 3% in the United States to 25% in Japan [14].

## Clinical Complications

The acute clinical complication of ulcers is bleeding and approximately occurs in 15%-20% of ulcers. Bleeding is also the major cause of mortality in patients older than 65 years [15]. Chronic symptoms include ulcer perforation and stricture formation. Recurrent ulcer disease, in particular from the pyloric and bulbar region, can lead to scarring with stricture formation and gastric outlet obstruction. In such patients, malignancy can be an underlying cause of the stricture. Hemorrhage is another frequent PUD complication and its incidence is increasing in comparison to perforation and stenosis [16]. These complications can occur in patients with peptic ulcer of any etiology and

are represented by symptoms such as abdominal pain, nausea, vomiting, loss of appetite, weight loss and fatigue.

## Etiology

Till the last decade it has been estimated that 95% of duodenal ulcer and 70% of gastric ulcer is attributed due to *H. pylori* [17]. About 14%–25% of gastric and duodenal ulcers are found to be associated with NSAID use [18]. Interaction data and randomized trial with NSAIDs and *H. pylori* eradication therapy revealed that the ulcer-inducing effects of both risk factors are cumulative [19-20]. However, their potential interaction in the induction of ulcer disease remains unidentified. Eradication of H pylori did not reduce the rate of ulcer relapse in existing long term NSAID users [21]. PUDs posse a multifactorial disease pathway majorly governed by acid disbalance and low mucosal defense leading to inflammation. This is represented by hypersection of hydrochloric acid and pepsin. This causes an imbalance between gastric luminal factors and degradation in the defensive function of the gastric mucosal barrier such as mucus, secretion of bicarbonate, mucosal blood flow, and epithelial cell defense. On invasion of acid and pepsin through a weakened area of the mucosal barrier leads to release of histamine. Histamine stimulates parietal cells to secrete more acid. With the continuation of this vicious cycle resulting in erosions to form the ulcer.

## Role of *H. Pylori* infection

H.pylori induced ulcer development is influenced by a variety of host and bacterial factors. Ulcers mostly occur at sites of most severe mucosal inflammation [2]. Decreased acid output, usually is the gastric transitional zone between corpus and antrum, give rise to gastric ulcer disease. If acid production is normal to high, the most severe inflammation usually is found in the distal stomach and proximal duodenum, giving rise to juxta-pyloric and duodenal ulcer disease. An individual's ultimate clinical outcome is dependent on the cytokine response and on the gastric acid secretion [22-23]. An increase in stimulated acid production predisposes to duodenal ulceration and decreased acid production predisposes to corpus gastritis or pangastritis which in turn predisposes to gastric ulceration, atrophic gastritis, and gastric carcinoma [22-23]. The intragastric distribution of gastritis is thought to be dependent on host genetic factors, bacterial virulence factors and environmental factors including age at onset of infection [23].

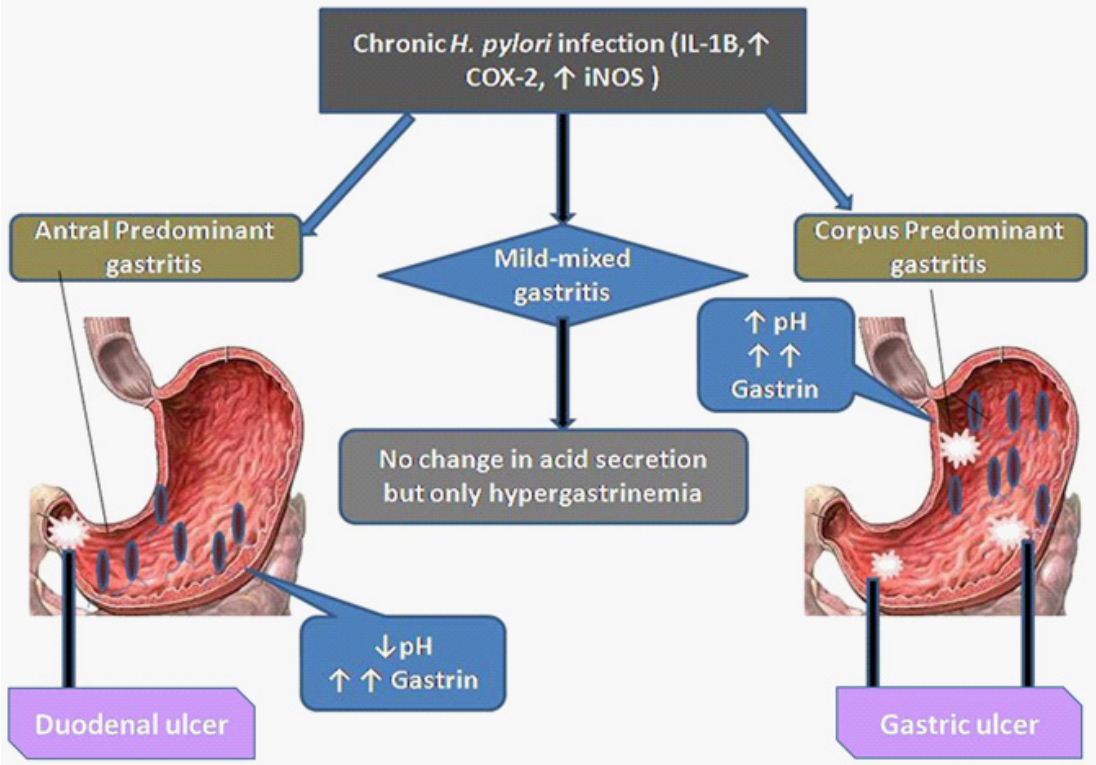


**Figure 1:** Depicting colonization of *H. pylori* in different regions of the stomach leading to various gastroduodenal diseases.

Duodenal ulcers are associated with *H. pylori*–induced antrum-predominant gastritis, decreased somatostatin levels and augmented gastrin and acid secretion [14,24]. Development of gastric metaplasia in the duodenum further allows bacterial colonization, thereby leading to duodenitis and epithelial damage. Gastric ulcers are associated with corpus gastritis, which is believed to damage the epithelium [24]. Eradication of the infection heals peptic ulcer disease, restores normal acid secretion and prevents ulcer relapse [25].

Host response plays a crucial role in *H. pylori* induced ulceration. The humoral immune system has only marginal relevance for protective immunity in *H. pylori* infection. *H. pylori* induce a Th1-polarized response that unfortunately does not result in clearance of the infection. *H. pylori* is thought to manipulate the host immune response and inflammation [26]. The key activator of the innate immune response is probably intracellular peptidoglycan [26]. *H. pylori* is capable of inhibiting phagocytosis by macrophages by an as-yet unknown mechanism. IL-10-producing T cells seem to be crucial in the control of inflammation and they enable the bacteria to persist in gastric mucosa [26]. Several cytokine genes have stable polymorphisms which are known to affect the level of cytokine production in response to *H. pylori* infection [27,26]. The best known of these is interleukin-1β, a potent proinflammatory cytokine and the most potent known inhibitor

of acid secretion [26]. These cytokine polymorphisms may contribute to the risk of gastric adenocarcinoma, but their contribution to the risk of peptic ulceration is conflicting [28-29].

## Role of NSAIDs

Severe ulcer complications and gastrointestinal damages have been associated with NSAIDs, since last two decades. The risk of these complications have been found to increase with geriatric population [30], previous history of peptic ulceration, and probably the first three months of NSAID treatment.. Endoscopic studies reported more gastric than duodenal ulcers associated with NSAID use, however, patients presenting with gastrointestinal bleeding on NSAIDs may have a similar frequency of gastric and duodenal ulceration. NSAIDs tend to influence the Cyclo-Oxygenase **(COX)** pathways which lead to the production of prostanoids (prostaglandins, prostacycline, and thromboxane). This impacts the mucosal protection by reducing the effectiveness of the mucus-bicarbonate barrier; gastric acid, and possibly also pepsin, plausibly causing damage. As most NSAIDs are also weak acids may also be a contributory factor in ulceration [31].

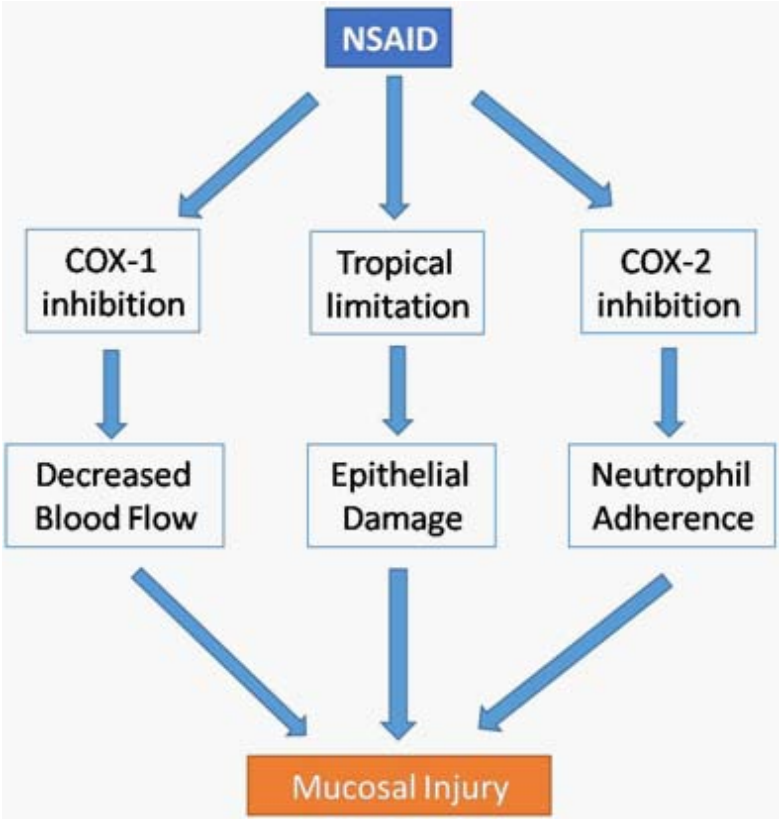


**Figure 2:** Pathogenesis of NSAIDs induced GI injury.

## MANAGEMENT OF PUDS

Clinical management of *H. pylori* infection and its associated morbidity, as well as related research, rely on the availability of practical and well-evaluated diagnostic test and treatments. Disease prevention may be possible by targeting the infection, either by eradication treatment or by preventing the establishment of the infection. Furthermore, it should be kept in mind that infection with *H. pylori* is more common in low-income countries and any tools for the management of the infection should thus preferably be accessible also in these underdeveloped countries.

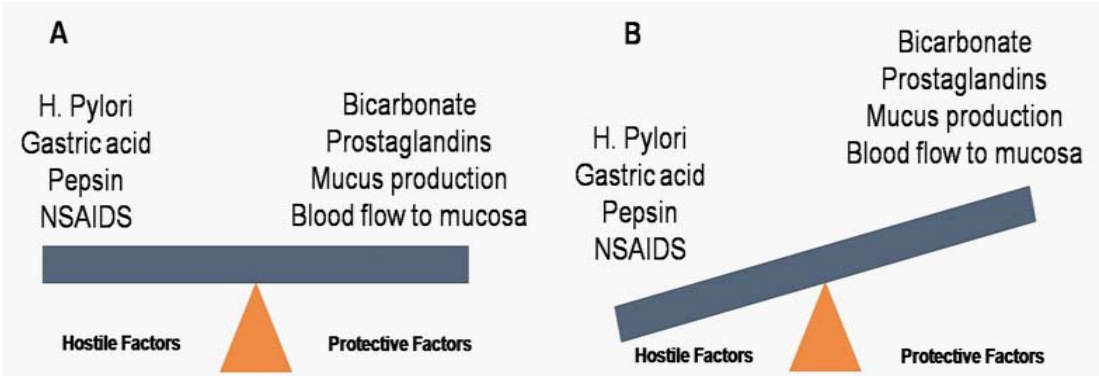


**Figure 3:** Management of PUDs.

## DIAGNOSIS

A fundamental principle of specific antimicrobial therapy is accurate diagnosis. Numerous validated methods to diagnose patients with *H. pylori* infection are currently in practice as it represents one of the most chronic diseases of humans. The diagnostics methods are broadly classified as:

i. Invasive method &

ii. Non-invasive method

### Invasive Tests

#### Endoscopy

Invasive methods of investigation include gastric biopsy taken at endoscopy for Rapid Urease Test **(RUT)**, bacterial culture, histology or the polymerase chain reaction. Genta and Graham (1994), reported a sensitivity of 100% with biopsy specimens taken from angularis mucosa of the stomach.

### Histology

Histological detection of *H. pylori* is facilitated by using conventional Haematoxylin & Eosin **(H&E)** and special stains such as the Warthin-Starry and modified Giemsa stains are also used

[32-33]. Histology provides useful information concerning the severity of gastritis and the possible presence of premalignant and malignant changes [34].

## Non-invasive method

### Serology

Infection with *H. pylori* elicits a systemic IgG atibody response that can be detected for diagnostic purposes [35]. Anti-*H. pylori* antibodies can be assessed with ELISA or western blot. The latter method has the advantage of characterizing the immune response towards different bacterial antigens. Serologic methods have proven especially valuable in screening large number of individuals in epidemiologic studies [36]. These tests are relatively rapid and simple to perform, and much less expensive than tests requiring endoscopic biopsies. Serology tests may be more accurate than the biopsy based assays, which are local and subject to a variety of sampling errors [37]. Serological tests show positive result in a patient with gastric atrophy in whom the number of H. pylori organisms is so small as to be undetectable by biopsy or breath test-based methods [38]. Major limitation of this test is that it has a limited role in confirming eradication of *H. pylori* infection because it takes 6-12 months for the IgG titers to fall by 50% or more of pre-treatment [37].

### Urea breath test

The 13C-Urea Breath Test **(UBT)** relies on the principle that 13C-labeled urea is hydrolyzed by the bacterial urease with the formation of 13CO2, which is detected in the exhaled breath [35]. An advantage of the UBT is its ability to detect active infection, but the performance of the test in young children has been debated.

# TREATMENT

Management of PUD has improved substantially following the introduction of PPIs and therapy for *H. pylori* eradication. This is reflected in the decrease in prevalence of *H. pylori*-associated PUD, the change in the proportion of *H. pylori*-positive PUD, and the lower proportion of *H. pylori* infection, particularly in complicated PUD. The continued occurrence of PUD is probably due, at least in part, to the widespread use of low-dose ASA and NSAIDs, especially in Western countries and among older patients and those with comorbidities. Use of these medications may also explain why the rate of hospitalizations for PUD complications has not decreased in some studies [11-12] and the general lack in reduction of mortality from PUD bleeding [39]. Use of traditional NSAIDs in Western countries has increased since the withdrawal of some cyclooxygenase-2-selective inhibitors and PPIs have been shown to produce a marked and consistent reduction in the risk of gastrointestinal symptoms in patients receiving NSAIDs and non-ASA anti-platelet agents [40]. The common occurrence of PUD in users of NSAID or low-dose ASA, despite wide availability of guidelines on the use of gastroprotective agents in NSAID users, is likely to be due to incomplete application of these guidelines in clinical practice and incomplete adherence of

patients to prescribed gastroprotective medication [41-44]. The discovery of the role of *H. pylori* in genesis of peptic ulcer disease has lead to a paradigm shift in the treatment of ulcer patients.

**Table 1:** PPI doses relating to evidence synthesis and recommendations in the original guideline [1].

| PI | Full/standard dose | Low dose (on-demand dose) | Double dose |
|---|---|---|---|
| Esomeprazole | 20 mg once a day | Not available | 40 mg once a day |
| Lansoprazole | 30 mg once a day | 15 mg once a day | 30 mg twice a day |
| Omeprazole | 20 mg once a day | 10 mg once a day | 40 mg once a day |
| Pantoprazole | 40 mg once a day | 20 mg once a day | 40 mg twice a day |
| Rabeprazole | 20 mg once a day | 10 mg once a day | 20 mg[2] twice a day |

**Table 2:** PPI doses for severe oesophagitis in this guideline update [1].

| PI | Full/standard dose | Low dose (on-demand dose) | High/double dose |
|---|---|---|---|
| Esomeprazole | 40 mg once a day | 20 mg once a day | 40 mg twice a day |
| Lansoprazole | 30 mg once a day | 15 mg once a day | 30 mg twice a day |
| Omeprazole | 40 mg once a day | 20 mg once a day | 40 mg twice a day |
| Pantoprazole | 40 mg once a day | 20 mg once a day | 40 mg twice a day |
| Rabeprazole | 20 mg once a day | 10 mg once a day | 20 mg twice a day |

**Table 3:** PPI doses for H pylori eradication therapy [1].

| PI | Dose |
|---|---|
| Esomeprazole | 20 mg |
| Lansoprazole | 30 mg |
| Omeprazole | 20–40 mg |
| Pantoprazole | 40 mg |
| Rabeprazole | 20 mg |

The relatively benign nature of *H. pylori* infection in the majority of infected individuals has elicited debate about how a positive diagnostic test should be handled. The argumentation has been further fueled by the suggested protective effect of the infection on esophageal adenocarcinoma. Nevertheless, general guidelines for treatment of the infection have been developed and continue to evolve [35, 14]. *H. pylori* eradication is strongly recommended for all patients with peptic ulcer disease, MALT lymphoma, atrophic gastritis, after gastric cancer resection and for first degree relatives of gastric cancer patients [45-46]. Furthermore, eradication treatment is advised for patients taking Non-Steroidal Anti-Inflammatory Drugs **(NSAIDS)**, which is an independent risk factor for peptic ulceration, and for GERD patients on long-term profound acid suppression, who can subsequently develop corpus atrophic gastritis. Patients presenting with persistent dyspepsia may also be offered eradication treatment, as it may lead to symptom improvement in a subset of patients [47-49].

*H. pylori* eradication therapy usually lasts for one to two weeks [50] and comprises of combination of antibiotics along with anti-secretory agents because acid impairs the efficiency of some antibiotics [35,14]. The therapeutic regimens have been traditionally divided into mono, dual, triple and quadruple therapy depending on the number of antimicrobials. The principal antimicrobials are clarithromycin, amoxicillin, metronidazole and tetracycline and the acid suppressant is usually a Proton Pump Inhibitor **(PPI)**. Ranitidine bismuth citrate combines antibacterial and antisecretory activities and can also be used.

In general, monotherapy is not recommended for the treatment of *H. pylori* infection due to poor clearance rates and problems of drug resistance [51-52]. Dual therapy with omeprazole and amoxicillin for 2 weeks showed promising results initially, with eradication rates up to 80% [53]. Triple therapy with two antibiotics (clarithromycin and amoxicillin) and a PPI is highly recommended treatment modality for the effective and successful eradication of *H. pylori* infection, but antibiotic resistance to particularly metronidazole and clarithromycin, is an increasing concern [35,14,52]. Figures from Indian studies quote an eradication rate of 67% with triple therapy, with healing of ulcers in 93% and improvement in clinical symptoms and gastritis in patients with non-ulcer dyspepsia [54].

Reinfection rates are generally considered to be low after successful eradication [55,35,14,56]. However, reinfection may be more common in young children [57,56] and in high prevalence settings [58-59]. Post- eradication reinfection rates of about 20% have been reported in adults in high prevalence communities [58-59], thus being comparable to the incidence in childhood. These reported high reinfection rates speak against a significant role of protective immunity after therapeutic eradication and indicate that prevention of acquisition is needed to attain long-term absence of infection in some high-prevalence settings.

## PREVENTION OF *H. PYLORI* ASSOCIATED DISEASE

Prevention of *H. pylori* associated disease benefits from predictions of who will become clinically ill. Accordingly, current treatment guidelines advise prophylactic *H. pylori* eradication for some individuals at higher risk for disease [35,14]. Some studies have also targeted high-risk population groups to study the effect of *H. pylori* eradication. Antibiotic treatment has been reported to increase regression of cancer precursor lesions [60-61]. And despite low power and a lack of studies, there are many evidences that support the hypothesis that *H. pylori* eradication may protect against gastric cancer [62-63] .Indiscriminate treatment of *H. pylori* infections has been proposed as an approach to limit the burden of *H. pylori* associated disease. The appropriateness of such a large-scale and crude intervention has been questioned due to uncertain full spectrum of possible harmful consequences, for example development of antibiotic resistance [35,14,52].

An alternative approach could be to target the acquisition or persistence of the infection, while limiting the use of antimicrobials. The role of *H. pylori* vaccine is uncertain given the common failure of the immune system to clear the infection and the apparently inadequate protective

immunity against infection [64,57-58]. A protective vaccine would also have to be administered at an early age before the acquisition of infection. At this age, an immature immune system may not respond sufficiently to immunization. Another approach could perhaps be a therapeutic vaccine that would circumvent problems with antibiotic resistance. There have been considerable efforts to develop safe and effective vaccines against *H. pylori*, but despite some encouraging results further work is warranted to bring about effective and safe candidates for humans [65]. Moreover, probiotics have been suggested to be capable of contributing to control *H. pylori* infection, but this area of research is in its infancy [66].

Preventing establishment of infection by interfering with transmission is a strategy that has been used in public health interventions against a variety of infections. Only a few trials have considered preventing the establishment of *H. pylori* infection by limiting the transmission. This can be partly explained by the fact that there is no apparent prevention strategy at present. The lack of thinkable interventions may be attributed to the seemingly multifaceted nature of *H. pylori* acquisition, intertwined with activities of daily life. There have also been attempts to detect a difference in the reinfection rates in children depending on whether the whole family unit received eradication therapy or not [55]. No significant difference was observed, however the authors acknowledged that the study was likely underpowered due to overall low re-infection rate.

Any future prevention strategies of *H. pylori*- associated disease should likely be primarily aimed at high-risk populations and target both the infection and other known risk factors. Antibiotic treatment is likely to play a central role in efforts to eliminate the infection. However, understanding and interfering with the acquisition or persistence of the infection by other means may become useful supplemental strategies. This is likely to be true in some low-income populations, where effective antibiotic regimens may be impaired by high cost, poor compliance, antibiotic resistance and high reinfection rates.

## CONCLUSION

Peptic ulcer disease remains a common condition, although reported incidence and prevalence are decreasing may be driven by decrease in *H. pylori* associated PUD. *H. pylori* infections and use of NSAIDs possess the highest risk of ulcer development, however, the changing trends show increase in risk due to augmented use of NSAIDs.

NSAID related ulcers can be healed while NSAIDs are continued by the use of H2-receptor antagonists in high doses, or more effectively by PPIs. PPIs were also found to be very effective with *H. pylori* induced ulceration, seven days treatment were reported to be helpful in the eradication therapy. The concomitant and sequential regimens are currently the best validated first-line therapeutic options. Hybrid therapy is another effective CAM-based alternative. One of the promising attempts to increase the efficacy of *H. pylori* treatments has been conjunction of probiotics with eradication regimens. Due to the rapid development of quinolone resistance,

levofloxacin-based regimens should be currently reserved as second-or-more-line treatment options. As efforts to improve empirical treatments continue, the fields of genotypic detection of *H. pylori* antimicrobial susceptibility and pharmacogenomics offer a fascinating new perspective. Prevention of NSAID related gastrointestinal problems may be achieved by identifying and if possible reducing risk factors, the co-prescription of prostaglandin analogues or acid suppressive drugs (especially proton pump inhibitors), or by using the currently being developed and promising COX-2 specific inhibitors.The development of COX-2 specific inhibitors offers the hope of real progress in producing much safer and effective NSAIDs.

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