

Prospectives of *Helicobacter pylori*

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ABSTRACT

Helicobacter pylori (*H. pylori*) is a gram negative bacteria whose infection is highly prevalent among the human population and leads to gastrointestinal tract related diseases (gastric and duodenal ulcers, mucosa associated tissue lymphoma and gastric adenocarcinoma). Most people with *H. pylori* infection will never have any signs or symptoms. While this bacterium infects 50% of the world's population, in Africa its prevalence reach as high as 80% as the infection is acquired during childhood. *H. pylori* eradication treatment is becoming more challenging due to increasing antimicrobial resistance. Treatment regimens are expected to overcome the in-

creasing prevalence of resistant strains of *H. pylori* and achieve a >90% eradication rate. Although treatment regimens provide acceptable *H. pylori* eradication rates, the regimens used should contribute to future resistance of *H. pylori* to antimicrobials and other therapies.

Keywords: *Helicobacter pylori*, Route of transmission, Thumb rules, Treatment regimen

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INTRODUCTION

Helicobacter pylori (*H. pylori*), previously known as Campylobacter pylori, are a spiral shaped bacteria which is indicated by the term 'Helico'. They are attached to or located just above the gastric mucosa (Tan VP and Wong BC, 2011). The significance of the *H. pylori* for the human diseases were first acknowledged at 1983. Nearly 60 percent of the world's adult population has been infected. Though they are asymptomatic, they can lead to peptic ulcers and gastritis, an inflammatory condition of the stomach, in some people (Amieva M and Peek Jr RM, 2016). Gastric infections caused by *H. pylori* is one of the most widespread infectious disease worldwide with an estimation of 40%-50% of the population (McNamara D, et al., 2002). Various diagnostic tests are available for the testing the presence of *H. pylori* in patients suffering with ulcer or dyspepsia. The commonly used tests are the evaluation of biopsy specimens during upper Gastrointestinal tract (GI) I endoscopy, the detection of serum anti-*H. pylori* antibodies and breathe tests with 13 C-labeled urea (Howden CW and Hunt RH, 1998; Drumm B, et al., 2000; Graham DY and Qureshi WA, 2001).

H. pylori is adapted to live in harsh acidic environment and so they are well suited to survive in the stomach. These bacteria are capable of changing their surrounding environment and it reduces the acidity of stomach so they could live there. The spiral shape of the bacteria helps in penetrating of the stomach lining, where they are protected by mucus from the body's immune system. These bacteria lead to stomach related problems (McNamara D, et al., 2002).

More than 80% of the people affected do not express any symptoms and it may also play an important role in the natural stomach ecology. Nearly 50%-75% of the worldwide population has been affected by *H. pylori* infection. Over 70% of the people are affected in the developing countries whereas only 25%-50% of the population are affected in the developed countries (Howden CW and Hunt RH, 1998). It is revealed in the annual report that the rate of the infection in Asia is 4.3%-13% greater than the West, where the infection rate is only 0.5%-2.5% (Drumm B, et al., 2000). Studies has shown that in Asia the prevalence is greater in the over populated countries like China(58%), South Korea(60%), Vietnam(75%), India(79%), Bangladesh(92%) than the less populated countries like Singapore(31%), Malaysia(36%), Japan(39%), Taiwan(55%) and Thailand(57%) (Graham DY and Qureshi WA, 2001).

Most of the children are affected by this infection from the par-

ents or siblings and they are also affected due to the transmission of the bacterium to the GI tract by oral cavity, by fecal-oral route or by human to human transmission (Zhao S, et al., 2014; Safavi M, et al., 2016). The *H. pylori* infection is most commonly associated with the lower socioeconomic background, poor diet and hygiene, over-crowding, ethnicity, ages and sex, as well as less educated level and geographic location, which plays a major role in the distribution of the infection (Rana R, et al., 2017).

Most affected person's are asymptomatic, for which the reason is not very clear, but some person's could be born with more resistant immune system. But when the symptoms occur, the may include:

- An ache or burning pain in your abdomen
- Abdominal pain that's worse when your stomach is empty
- Nausea
- Loss of appetite
- Frequent burping
- Bloating
- Unintentional weight loss

H. pylori can lead to various upper gastrointestinal disorders such as gastric inflammation (gastritis), heartburn, gastro esophageal reflux disease, gastric duodenal ulcer disease, gastric cancer and Mucosa-Associated Lymphoid Tissue (MALT). Several eradication measures are available to treat the infection caused by *H. pylori* and one of the most widely used method is the several combined antibiotics, such as amoxicillin plus clarithromycin or metronidazole with a proton-pump inhibitor. Nowadays, the main problems faced towards *H. pylori* infection is antibiotic resistance, patients compliance and intolerance to therapeutic regimens. Antibiotic resistance is a major concern as the *H. pylori* becomes resistant to drugs and thus the treatment fails (Stollman NH and Graham DY, 2014). This resistance can be caused due to poor drug penetration, low drug concentration, short gastric residence time and also the antibiotic resistance represent a significant health care burden on the society. Patient compliance also becomes a problem due to poor stability of antibiotics in gastric content which requires frequent administration of the antibiotics (Pacífico L, et al., 2010; Carraher S, et al., 2013). The different therapies used for the treatment of *H. pylori* infection are standard, sequential, quadruple, concomitant and levofloxacin therapy. These therapies are best of the treatments and assure high cure rate. Though, recently standard triple therapy has shown reduced efficacy due to antibiotic resistance. Bismuth quadruple, concom-

itant, sequential and levofloxacin therapies are currently better than standard therapy that is providing promoted efficacy (Graham DY B, *et al.*, 2014). The last few decades has been proved that the eradication of this infection has been standardized but the resistance to therapeutic regimen poses as a growing problem. The intention of this paper is to provide an appraisal of the most effective, current treatments that are readily available for *H. pylori*, and also to speculate on the potential for newer approaches in treatment and prophylaxis in the future (Figure 1).

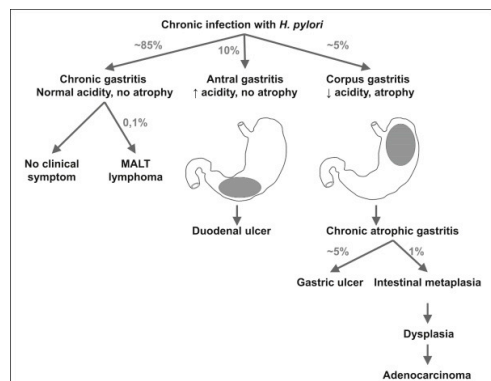


Figure 1: *Helicobacter pylori* infection

ROUTE OF TRANSMISSION

The transmission mechanism of *H. pylori* are still not well defined. The known factor is that the *H. pylori* travels from mouth to esophagus. The most likely modes of transmission are oral-oral and fecal-oral routes. Iatrogenic transmission is a rarely reported route. And then role of insect vectors is yet to be clarified.

Oral-oral transmission

This method has not been confirmed as of yet. *H. pylori* has been identified in dental plaque and has been rarely cultured in the buccal region (Hardo PG, *et al.*, 1995). Even then, the incidence of the infection has not been reported in hygienists and dentists much frequently, despite the fact that they are experiencing occupational exposure to oral aerosols. But on the either hand, gastroenterologists are reported to have higher prevalence than age-matched controls; 52%, compared with 21%. These changes were mostly observed in older gastroenterologists, who did not follow the necessary precautions in their early stages of practice (Mitchell HM, *et al.*, 1989). *H. pylori* was also cultivated from the vomit and saliva from healthy infected volunteers (Parsonnet J, *et al.*, 1999).

Fecal-oral transmission

This method is also possible. In the developing countries, water contamination serves as a source of organism exposure. Polymerase Chain Reaction (PCR) techniques were performed to confirm the presence and growth of *H. pylori* colony in the municipal water supplies and the other studies also suggests that these organism can survive in water for several days (Hulten KR, *et al.*, 1996). These organisms have also been found in the stools of children from Gambia and West Africa, where there is 99% prevalence of infection (Thomas JE, *et al.*, 1992). Intra-familial clustering of infection also supports and enhances person to person spread. The young children who gets affected by the *H. pylori* infection are most likely to have an already affected parent or siblings (Drumm B, *et al.*, 1990). However, the isolates may not be the same within each family member, implying the involvement of other sources.

Iatrogenic transmission

This type of spread can be documented. A contaminated pH probe can affect 17/34 consecutive patients (Ramsey EJ, *et al.*, 1979). In another

study, it is known that a volunteer was infected with a contaminated endoscope. The risk of this transmission has been estimated at 4/1000 endoscopies in the developed world.

Vector transmission

Non human vectors plays an important role. Recent studies has also suggested that the domestic cats may also act as a carrier of *H. pylori* but it remains as a controversial fact (Handt LK, *et al.*, 1995). Though isolation of organisms in cat saliva suggests transmission of *H. pylori* studies have also shown that house flies can not only carry the bacterium but also harbor them (Grübel P, *et al.*, 1997). Evidence of *H. pylori* has been gathered in the house flies in the developing countries as well as in the United States, but it may also be due to environmental contamination rather than mode of transmission (Grubel P and Huang L, 1998).

Reinfection

Reinfection after cure is unusual in developed countries, and is estimated to be less than 1% per year (Parsonnet J, 1995). Recurrence of infection most likely represents recrudescence. Reinfection rates are higher in developing countries and are approximately 8%-15% (Rollan A, *et al.*, 2000). However, it is not yet clear whether it is due to inadequate monitoring. In developed countries it has become an uncommon occurrence in children and it may be due to improved sanitary and hygiene conditions.

Diseases associated with *H. pylori*

The *H. pylori* condition is associated with gastritis, Non-Ulcer Dyspepsia (NUD), duodenal ulcer, gastric ulcer, gastric cancer, gastric lymphoma of Mucosa Associated Lymphoid Tissue (MALT) and even coronary heart disease. It is also proved that they are also the cause of almost all Duodenal Ulcers (DU) and chronic benign Gastric Ulcers (GU) which are not associated with Nonsteroidal Anti-Inflammatory Drugs (NSAID). More than 95% of DU and 90% of GU are associated with *H. pylori* infection and there is a dramatic decrease in their relapse rate after the *H. pylori* eradication. As for now there is no reliable evidence that NUD symptoms are due to *H. pylori* infection. The prevalence of this disease can be compared between a healthy individual and the patients who shows symptoms of NUD. Further studies are necessary to eradicate the *H. pylori* completely in NUD (Rogha M, *et al.*, 2012; Rogha M, *et al.*, 2012).

Rules of thumb for optimizing *Helicobacter pylori* treatment

1. Use four drugs
2. Use maximal acid inhibition
3. Treat for 2 weeks
4. Do not repeat antibiotics after treatment failure
5. If your treatment works locally, keep using it.

Rule of thumb 1: Use four drugs: Overall, three main groups of quadruple therapies have been assessed in the literature:

- (a) adding metronidazole to classical clarithromycin-containing triple therapy,
- (b) classical PPI-bismuth-metronidazole-tetracycline quadruple therapy, and
- (c) adding bismuth to triple therapy.

Rule of thumb 2: Use maximal acid inhibition: *H. pylori* needs an acidic medium to survive due to its production of NH₃ which needs to be neutralized by acid. High gastric pH allows the replication of the bacterium. Higher PPI doses to adequately control gastric pH Many meta-analyses have shown that increasing acid inhibition raises cure rates with *H. pylori* triple therapy.

Rule of thumb 3: Treat for 2 weeks: Since the first meta-analysis was published (Hwang JJ, *et al.*, 2015), it has been clearly established that increasing the length of triple therapy from 7 to 14 days increases cure rates. 14-day concomitant therapies consistently achieved cure rates of around 90%, whereas 10-day therapies were somewhat less reliable.

Rule of thumb 4: Do not repeat antibiotics after treatment failure: Repeating of certain antibiotics only when it is indispensable and in the setting of 14-day quadruple therapies. Thus, it helps in the forming of reduced resistance against the antibiotics and so the antibiotic can be used repeatedly without decrease in the efficacy. Therefore, certain antibiotics like bismuth, amoxicillin and tetracycline can be used in the same patients despite the fact that the previous treatment has failed. These data should be taken into consideration when choosing a rescue therapy among the various consensus recommendations.

Rule of thumb 5: If your treatment works locally, keep using it: There is no defined worldwide gold standard treatment. Most of the studies have been using combinations of the drugs mentioned above. However, recommendations should be locally adapted. As long as monitoring of cure rates confirm high effectiveness, there is no reason to change to more complicated schedules (Saad R, *et al.*, 2005; McCarthy C, *et al.*, 1995).

TREATMENT

First-line therapy

The current first-line treatment for *H. pylori* includes a PPI in combination with the antibiotics clarithromycin, metronidazole or amoxicillin for a duration of 7, 10 or 14 days (Hwang JJ, *et al.*, 2015; Dos Santos AA and Carvalho AA, 2015). Due to high resistance of antibiotics gastroenterologists proposed a novel regimen, called 'sequential therapy', for regions with high rates of clarithromycin resistance (>20%) (Zullo A, *et al.*, 2003).

Second- and third-line therapy

Several reports have confirmed that the first-line therapy. Accordingly, after several reports of failures in first-line therapy, 10 days of bismuth-containing quadruple therapy or levofloxacin-containing triple therapy as second-line treatment was increasingly recommended (Song Z, *et al.*, 2016). It has been observed that there is a limit for prescribed antibiotics in second- and third-line therapies. It has been shown that extending the duration from 1 week to 2 weeks in second-line therapy can increase the efficacy of treatment (Chuah SK, *et al.*, 2012; Miehlke S, *et al.*, 2011; Tai WC, *et al.*, 2013). It was logical to redesign the regimens with different antibiotics such as levofloxacin or rifabutin due to *H. pylori* resistance to antibiotics (metronidazole and clarithromycin) (Chuah SK, *et al.*, 2011).

Probiotics

A living microbe that may have a positive effect towards eradicating pathogens is called probiotics. The main explanations for this theory are: decreasing side effects following therapy; and (ii) increasing eradication rate. However, a long list of examinations is required to accurately identify which probiotic strains, delivery route and administered dose can provide the best probiotic panel in the clinical setting (Lesbros-Pantoflickova D, *et al.*, 2007; Schrezenmeir J and de Vrese M, 2001). Mostly it is suggested that the probiotics should be given as an adjuvant along with the regularly prescribed antibiotic therapy to provide better therapeutic effectiveness. At the least, they reduce the side effects which occur followed by chemotherapy (Rostami N, *et al.*, 2008; Fallone CA, *et al.*, 2016; Gatta L, *et al.*, 2018).

A number of mechanisms have been anticipated for probiotic efficacy against *H. pylori*. Probiotic bacteria can modulate *H. pylori* activity by either immunological (e.g., increment of serum IgA and reduction

in cytokine profiles such as IL-6) or non-immunological mechanisms (antagonism and competition with potential pathogen (Ayala G, *et al.*, 2014; Patel A, *et al.*, 2014; Yang YJ and Sheu BS, 2012; Ljungh A and Wadstrom T, 2006). The use of probiotics, as adjuvant therapy, appears promising for the current *H. pylori* eradication treatment, in order to reduce the frequency of antibiotic induced side-effects, though it still requires optimization (Zojaji H, *et al.*, 2013; Khodadad A, *et al.*, 2013). Briefly, we are still in the early stages of using probiotics against *H. pylori* infection (Table 1).

Table 1: Evidence based treatment regimens (Fallone CA, *et al.*, 2016; Gatta L, *et al.*, 2018; Ayala G, *et al.*, 2014)

Treatment	Drugs used	Duration of use	No of days used
Clarithromycin based therapy	PPI, clarithromycin, and amoxicillin	Twice daily (for all antibiotics)	14
Bismuth based therapy	PPI, bismuth, tetracycline, and nitroimidazole	Four times daily for all antibiotics	10 to 14
Concomitant therapy	PPI, clarithromycin, amoxicillin, and nitroimidazole	Once daily for all antibiotics	10 to 14
Sequential therapy	PPI and amoxicillin; then PPI, clarithromycin, and nitroimidazole	Twice daily for all antibiotics	7; 7
Hybrid therapy	PPI and amoxicillin; then PPI, amoxicillin, clarithromycin, and nitroimidazole	Twice daily for all antibiotics	7; 7
Levofloxacin based therapy	PPI, levofloxacin and amoxicillin	Once daily Twice daily	10-14
Fluoroquinolone based sequential therapy	PPI and amoxicillin; then PPI, levofloxacin, and Nitroimidazole	Twice daily for all antibiotics	5-7;5-7

Herbal therapy

Recently a phytomedicine has a complementary function for *Helicobacter pylori*. Many plant extracts, partially purified reactions and natural compounds with the anti-*H. pylori* activity has been reported (Safavi M, *et al.*, 2015; Shahani S, *et al.*, 2012; Wang YC, 2014; Falsafi T, *et al.*, 2015). Some bioactive compounds from medicinal plants with anti-*H. pylori* activity include carvacrol (Takabayashi F, *et al.*, 2004), polyphenolic catechins (Ali SM, *et al.*, 2005), tannins (Ramadan MA and Safwat NA, 2009), cinnamaldehyde, eugenol (Fukai T, *et al.*, 2002), quercetin (Mahady GB, *et al.*, 2003), licoricidin, licoisoflavone B (Dabos KJ, *et al.*, 2010), Berberine, sanguinarine, chelerythrine, protopine, β -hydrastine (Paraschos S, *et al.*, 2007), mastic (Wang YC and Huang TL, 2005), plumbagin (Bisignano C, *et al.*, 2012), protocathechuic acid. This may be more beneficial if the medicinal plants in combination with present antibiotic regimens are used to develop more effective eradication regimens (Tadjrobehkar O and Abdollahi H, 2014). However, mode of action, potential cytotoxicity and benefits of herbal medicine are complex, incomplete and confusing (Vale FF and Oleastro M, 2014).

Photodynamic therapy

Photodynamic inactivation of microorganisms is on the basis of the combination of a sensitizer or photo sensitizer and harmless visible light of an appropriate wavelength. Recently, some *in vitro* (Choi SS, *et al.*, 2010; Simon C, *et al.*, 2014; Hamblin MR, *et al.*, 2005) and *in vivo* (Lembo AJ, *et al.*, 2009; Ganz RA, *et al.*, 2005) studies to develop anti-*H. pylori* photodynamic therapy for the eradication of *H. pylori* were

successful (Maisch T, *et al.*, 2007). It is necessary to perform *in vivo* photodynamic therapy and indicate the limitations and effectiveness of this novel technique with less cost, side effects and ease of administration (Calvino-Fernández M, *et al.*, 2013; Choi SS, *et al.*, 2010).

CONCLUSION

Although oral delivery is considered to be the most promising administration route due to its specific advantages, it faces substantial challenges that need to be addressed before oral systems can be commercially available for the delivery of biopharmaceuticals. Fabrication protocols of the carriers should adequately avoid any destructive on the drug molecules, especially for biopharmaceutical encapsulation/delivery. Concurrently, the delivery material, design, size and polydispersity must be accurately controlled, due to their significant influence on treatment efficacy. Oral carriers deal with various biological barriers to successfully deliver drugs. Sustained delivery, microencapsulation have also been major focuses in oral delivery studies. Nonetheless, the most significant issue against the commercialization of the oral systems is their low throughput. This review introduced the most promising solutions recently proposed for each barrier, which point to a positive progress in the field of oral drug delivery. Considering the recent achievements in the case of technological challenges, we believe that future research in this field will mainly target biological barriers, especially the barriers associated with tissues. The main advantages of oral delivery systems, include sustained delivery, interaction with mucus and the capability for solid formulations that preserve pharmaceuticals, still making this the most attractive administration route for pharmaceuticals.

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