A REVIEW OF HELICOBACTER PYLORI INFECTION DISEASES, ANTIBIOTIC RESISTANCE AND DIAGNOSIS

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ABSTRACT

Objective: The aim of the study was designed to assess the mechanisms of antibiotic resistance in Helicobacter pylori, affecting disease by this infection and diagnostic methods which are used to detect H. pylori.

Methods: A wide literature search was performed using PubMed, Medline, Cinahl, Embase, Educational Resources Information Center, PsycINFO, Google Scholar, Scopus, and Web of Science, and review of appropriate epidemiologic studies conducted from 1995 to 2017 for studies fully published investigating a contribution between H. pylori infection, antibiotic resistance, and diagnosis of H. pylori infection.

Results: H. pylori infection is extremely contributed to the main symptoms and death that is currently affecting 50–75% of the people in the world. It is more affected in developing countries compared to developed countries. These infections are regarded to be the most important reasons for gastric cancer, peptic ulcer, chronic gastritis, duodenal ulcer, mucosa-associated lymphoid tissue lymphomas, and gastric adenocarcinoma. About 90–100% of duodenal ulcers and 60–90% of gastric ulcers were associated with H. pylori infections. At present, antibiotic resistance is a growing problem for the eradication of H. pylori infection; it contains metronidazole, amoxicillin, clarithromycin, and levofloxacin resistance. Diagnosis of H. pylori infection is a crucial part for the better treatment of those diseases. Different types of testing method for H. pylori infection are used including invasive (endoscopic image, histology, rapid urease test, and culture) and non-invasive (urea breath test, stool antigen test, and serological).

Conclusion: H. pylori antibiotic resistance is the major contributor to the failure of H. pylori treatment. Appropriate diagnostic method selected in detecting H. pylori antibiotic resistance may lead to reduced treatment failures and less antibiotic resistance.

Keywords: Helicobacter pylori, Gastric cancer, Peptic ulcer, Antibiotic resistance, Invasive test, Non-invasive test.

INTRODUCTION

Helicobacter pylori is a Gram-negative bacterium which is found in the mucus layer and the mucosa of the stomach, and it is regarded to be associated with stomach diseases such as chronic gastritis, gastric ulcers, duodenal ulcers, and gastric cancer [1-4]. It has been recently found that over 90% of duodenal ulcers and 50–70% of benign gastric ulcer are associated with H. pylori infection. It has been recently found that over 90% of duodenal ulcers and 50–70% of benign gastric ulcers are associated with H. pylori infection [5,6]. This infection could be regarded as one of most universal infectious agent where is exist to determine diverse disease [7]. It is also spread in worldwide and affecting different types of factors such as environmental factors, virulence factors, and host factors, which caused by gastric cancer, chronic gastritis, and peptic ulcer diseases (PUD) (Fig. 1) [8].

H. pylori is associated with different diseases such as gastritis, DU disease of the stomach and duodenum, gastric adenocarcinoma, and low-grade gastric lymphoma growing from mucosa-associated lymphoid tissue (MALT) [9,10]. It is approximately 50%–75% affected with respective infection globally whereby in the developing countries 70% of people are affected, whereas the percentage little lowers, 25–50% in the developed countries [11,12]. Present studies have demonstrated that H. pylori infection is also associated in chronic bacterial infection worldwide, which is affected almost 50% of people in the developed countries and about 190% of people in developing countries [13]. The prevalence of H. pylori infection is almost 50% in the worldwide and this infection is highly affected in developing countries (80–90%), as well as, the annual incidence of H. pylori infection is influenced in developing countries (4–15%) than industrialized countries (0.5%) [14,15]. Present studies revealed that H. pylori infection is associated with cardiovascular diseases and atherosclerosis [16].

A study demonstrated that H. pylori is infected in human gastric mucosa of more than 50% of people in the world which is caused by long-term colonization and inflammation as a produce to a variety of diseases, from gastritis to PU (gastric ulcer and duodenal ulcer), gastric cancer, and the MALT lymphoma [17]. This infection is existed in beneath the gastric mucous layer, nearby to the gastric epithelial cells [18]. Awork reported that H. pylori seropositivity is a risk issue for gastric, colorectal, pancreas, and hepatobiliary cancers and an improved seroprevalence rate was also found in different respiratory ailment such as chronic bronchitis, asthma, and pulmonary tuberculosis [19].

Nowadays, antibiotic resistance is an international healthiness problem which is major cause of treatment failures in H. pylori infection. Prevalence of H. pylori antibiotic resistance is not the same in all over the world because it depends on geographical variations [20]. It is increased in worldwide, and most of drugs are resistance for the eradication of H. pylori infection such as metronidazole (MTZ), clarithromycin (CLA), and amoxicillin (AMX) due to decreased efficacy of drug [21]. Eradication of H. pylori infection failure is main reason of one or more two antibiotic resistances and genetic alteration and biofilm formation that is associated with H. pylori infection [22,23]. At present, H. pylori infection is complicated to eradicate as failure rate exist 10–40% due to increasing resistance of the microbe to conventional antimicrobial agents [24]. Therefore, improving antibiotic resistance rates and lower eradication rates are the main troubles in H. pylori infections treatment.

Diagnosis of H. pylori infection is a crucial part of the better treatment of many gastroduodenal diseases [25]. There are two types of a diagnostic image, histology, rapid urease test, and culture) and non-invasive (urea breath test, stool antigen test, and serological).
in an endoscopic image, histology, rapid urease test, culture, and molecular methods, as well as non-invasive diagnostic tests, including urea breath test (UBT), stool antigen test, serological, and molecular examinations [26]. It has proved that for primary diagnosis of *H. pylori* infection, rapid urease test, and tissue staining with gastric tissues attained by endoscopy of the upper gastrointestinal tract is necessary to confirm *H. pylori* infection in both adults and children [27]. Therefore, this study major purposed to provide a cause of antimicrobial resistance in *H. pylori* infection, disease and which methods are best for *H. pylori* infection test.

**METHODS**

During the primary search, different medical terms and phrases related to *H. pylori* infection, diseases, epidemiology, antibiotic resistance, and diagnosis of *H. pylori* infection were single or in various combinations searched from various databases including PubMed, Medline, Cinahl, Embase, Educational Resources Information Center, Google Scholar, PsycINFO, Scopus, and Web of Science, to identify articles containing related information on the topic of study. All relevant articles published between 1995 and 2017 were identified and selected for further review.

Data analysis and results

A total of 1045 related articles were identified through electronic search, while 10 were through manual methods, and preliminary screening of the articles revealed that 431 were duplicates, hence excluded from further analysis.

The titles of selected articles and abstracts were again checked for relevancy, and 47 were eligible for full-text screening, after which 10 of the publications qualified for the last stage of the selection process, as shown in Fig. 2.

Details descriptions of the papers were then carried out based on the following criteria: (1) Reported by gastric cancer and PU; (2) investigation of the diagnostic methods such as invasive (endoscopic image, histology, rapid urease test, and culture) and non-invasive (UBT, stool antigen test, and serological); and (3) antibiotic resistance such as MTZ, AMX, CLA, and levofloxacin resistance.

**Epidemiology of *H. pylori* infection**

*H. pylori* is one of the general bacterial pathogens in humans which consist of small, curved, highly motile, and remains as colonies in the mucus layer of the human stomach (Fig. 3). It is continuing existent in the stomach which is occurred early in the childhood [28-30]. In developing countries, this infection is rapidly increased and started from first 5 years in life after that persistently exist in life. This infection is transmitted from person to person through oral-oral or fecal-oral routes during childhood in the past decades [31]. A study demonstrated that *H. pylori* is a helical or curved bacillus that colonizes the gastric mucosa and also transmitted in nonculturable coccoid [32]. It was first exposed and acknowledged in 1984 by Marshall and Warren, where it was found in gastric mucosa [33,34]. Recent studies revealed that this infection is prevalent in men rural area, low socioeconomic standard, low educational levels, and crowded places. It was reported that the incidence in Egypt was approximately 50% in children ≤3 years old and 90% in adults [35].

**Gastric cancer**

*H. pylori* is the most crucial etiologic aspect for gastric cancer which affected about 50% of people, and people’s deaths are more than 720,000/year globally [36]. It is usually infected malignancies or carcinoma worldwide which is mainly colonized in the human stomach coexisted in about 60,000 years age [37]. Gastric cancer with *H. pylori* infection is more prevalent in developing countries than in developed countries [38]. It is a major global health warning and the third leading cause of cancer death worldwide, caused by *H. pylori* infection, the Gram-negative, and microaerophilic bacterium [39,40].

Recently, the prevalence rate of gastric cancer is higher in male than female. Some researchers believed that the low occurrence of *H. pylori*...
infection consequence of low incidence of gastric cancer, but geographic variation in gastric cancer prevalence rates cannot be similar describe in *H. pylori* prevalence. For instance, high populations of Africa and India have a higher prevalence rate of *H. pylori* infection but a lower incidence of gastric cancer [41]. Most researchers suggested that the pathogenesis of human gastric cancer is a multi-factorial and multistage method and is associated with cytokine gene polymorphisms which are progress gastric cancer with *H. pylori* [42]. In recent studies exposed that gastric cancer is the fourth largest part of malignancy in the earth that is attributed to 63% gastric cancer [7].

**PU disease (PUD)**

PUD is a common illness which is associated with *H. pylori* infection and lifespan incidence rate of approximately 10%. The prevalence rate of *H. pylori* infection with PUD is range from 50% to 70% for aged patients, as well as *H. pylori* with a duodenal ulcer is present in 90–100% of patients, and for gastric ulcer is represent 60%–90% of patients [43]. Recently, studies have shown that 90% of patients with PUD are infected with this infection [44]. It is found that *H. pylori* distributed within the lesser curvature, in particular along with the transitional zone between corpus and antrum, while duodenal ulcers generally appeared in the duodenal bulb [7]. On the other hands, gastric cancer is increased when people are administered NSAID drugs, while duodenal ulcer is increased when improving acid secretion in the stomach [45]. Currently reported that PU is consists of gastric and duodenal ulcers which are called mucosal defects. On the other hands, in Western countries, duodenal ulcers are four-fold, and it is going on duodenal ulcers which are called mucosal defects. On the other hands, the stomach [45]. Currently reported that PU is consists of gastric and duodenal ulcers which are called mucosal defects. On the other hands, in Western countries, duodenal ulcers are four-fold, and it is going on 20 and 50 years of period, while gastric ulcers are mainly happened in >40 years old [29]. Present studies have shown that PU is generally caused by stomach acid and digestive enzyme pepisin that is defects in gastric or duodenal mucosa because of imbalance between acid amount and mucus defense which results in damage of lining in the stomach [46].

**MTZ resistance**

MTZ is a 5-nitromidazole antibiotic that is used for the treatment of *H. pylori* infection and other infection such as parasitic infections, anaerobic, and microaerophilic bacterial infections. MTZ resistance with *H. pylori* is more affected in developing countries than in developed countries. It is associated with null mutation ferredoxin (fdx A) that is contributed in resistance to MTZ due to amino acid substitution mutations [20]. Null mutations in MTZ-resistance isolated by W (209) R substitution by polymerase chain reaction (PCR) amplification of rdxA and RND family of efflux pumps [47,48]. It has been reported that mutations are stopped codons or substitutions inactivate the rdxA gene, as a result, the fxdA gene improves resistance and represents mutations with rdxA [49].

**AMX resistance**

AMX is a broadspectrum and β-lactams antibiotics. It’s binding site penicillin-binding proteins (PBPs) in the bacterial cell wall and inhibits cell division; which is observed in E. coli spp and Salmonella spp. [20]. It has demonstrated that antibiotic resistance is a major cause of alterations in PBP and decreased membrane permeability of antibiotics into the bacterial cell; and mutations PBP1A, PBP2, hefC, hopC, and hof gene have been contributed to *H. pylori*-resistant strains [50].

**CLA resistance**

CLA (6-O-methyl erythromycin) (CLA) is a macrolide antibiotic which is binding to peptidyl tRNA to domain V the 235 rRNA molecule in ribosomes and blocking bacterial protein synthesis [22,51]. It is contributed with A-to-G transition at position 2142 (A2142G) or 2143 (A2143G). PCR method is used to investigate in 23S rRNA gene mutations in CLA-resistant *H. pylori*, as well as showed that A2142G mutation is lower than A2143G mutation [52]. It is also found that other mutations such as A2115G, G2141A, C2147T, T2190C, C2195T, A2223G, and C2694A could lead to being improving CLA resistance [50]. It has proposed that those all mutations are decreased in the binding site of the drug result in CLA resistance [53].

**Tetracycline resistance**

Tetracycline is an antibiotic that is combined in aminoacyl-tRNA to the ribosomal acceptor (A) and blocking bacterial protein synthesis, and antibiotic resistance is associated with mutations in 16S rRNA-encoding genes which are detected by PCR method [7]. Antibiotic resistance to tetracycline is the main reason improved energy-dependent efflux of tetracycline that decreases the intracellular concentration of tetracycline and mediated ribosomal protection proteins. It has been also reported that mechanism of antibiotics resistance is declining the affinity of ribosomes for tetracycline, enzymatic inactivation of tetracycline, and point mutations in the 16S rRNA genes which is influencing the binding site of tetracycline [50].

**Levoﬂoxacin resistance**

Mechanism of levoﬂoxacin resistance is one kind of gyrA mutation gene which is connected to DNA gyrase code and macrolides. GyrA mutation gene prevents the inhibition of chromosome replication of the bacterium when observed in the presence of drug [50,53].

**Endoscopic invasive test for *H. pylori***

The endoscopic test is associated with identifying *H. pylori*-associated diseases, such as PUD, atrophic gastritis, MALT lymphoma, and gastric cancer. It is also used to achieve specimen biopsy from gastric mucosa. Antrum and the corpus is favorable biopsy site for *H. pylori* infection in most situations, but corpus biopsy is higher biopsy for patients with antral atrophy or intestinal metaplasia to remove false negative results [26]. Recently, studies have shown that maximum gastric mucous is redness and mucosal swelling, and it is not specifically used detection of *H. pylori* infection due to provide limited value in endoscopy diagnosis [54]. It has been revealed that endoscopy test is improving the diagnostic process for gastric mucosa; whereas it might be time-consuming and not provide better results than other invasive tests [55].

**Histology invasive test**

Histology is the first standard method used for the detection of *H. pylori* infection [26]. In the presence of representative bacteria between the inflammatory reaction in the tissue, slides are measured as a diagnostic test for *H. pylori* infection. Studies reported that
different types of stains are used for detection of H. pylori infection such as Giemsa, Acridine O, Warthin Starry, Hp silver stain, Dieterle, Gimenez, and McMullen. The hematoxylin and eosin stain used to detect inflammation with bacteria. Giemsa stain is more reasonable in detecting H. pylori because it is simple, high sensitivity, and less expensive [56]. Some studies have reported that this test is used to determine histological chronic or chronic active inflammation (gastritis), atrophy, and intestinal metaplasia, but the major problem is high observer-dependency, relatively long waiting time for result, the requirement of specialized skills for performance and relatively high cost for this test [45].

Recent studies demonstrated that it provides critical information related to mucosa such as severity of inflammation, intestinal metaplasia, glandular atrophy, dysplasia, and neoplasia as well as collected antrum and corpus biopsies which indicates sampling from 5 biopsy sites. Corpus biopsy attained from the smaller curvature of the corpus about 4 cm proximal such as angulus and antrum (both within 2–3 cm of the pylorus); and greater curvature of the corpus approximately 8 cm such as cardia and incisura angularis [57].

**Fluorescent in situ hybridization** is a new manner for histology invasive test that is accepted detection of a specific bacterial factor such as CLA resistance. This method is used to protein-labeled oligonucleotide probes that target a specific gene such as 16S and 23S ribosomal RNA genes, but this method is laborious, expensive, and not used in clinical practice. It is revealed that the histology test is provided in the historical record and evaluated in gastritis, atrophy, and incisura metaplasia (Fig. 5) [45].

**Rapid urease test (RUT) invasive test**

At present, rapid urease test is mostly used in the identification of H. pylori infection due to low-cost, rapid, easy to complete, extremely precise, and widely existing [26]. Current studies have shown that in this infection, urease enzyme converted to urea to release CO$_2$ and NH$_3$. Detection of urease production has been used as a surrogate marker for the detection of the bacterium in antral biopsies and the presence of H. pylori in biopsy specimen converts the urea test reagent to ammonia, as a result, increase in the pH and a color changes on the pH indicator. The RUT sensitivity influenced the number of bacteria in the biopsy and presence of blood; at least 10000 cells are needed for a positive result [57]. Also known as campylobacter-like organism test, this test has good sensitivity (80–100%) and specificity (97–99%) in diagnosing H. pylori (Fig. 6) [17,56,58]. Studies have showed that this test, however, cannot be used to assess gastritis [45].

**Culture invasive test**

The culture test is a gold standard method for detection of H. pylori infection, but this test is difficult to perform due to costly, time-consuming and needs for special media. It is used to recognize the antibiotic susceptibility of H. pylori in clinical practice [5].

**PCR**

PCR is a molecular method which is used to investigate amplifies a fragment of a gene specific for the H. pylori, for example, vacA and cagA gene sequences, 16S rNA, 23SrRNA, DNA gynase, bacterial genotypes, study pattern of antibiotic resistance, and H. pylori transmission [45]. Recently, studies have demonstrated that the PCR can be performed on stool and tissue specimen and assists identify genes related to antibiotic resistance and virulence [59]. Studies have reported that PCR is used to detect bacterium, pathogenic genes, and specific mutations contributed with antimicrobial resistance [60]. It has also found that PCR method is used to detect of H. pylori infection and recognize the exact mutations in the 23S rRNA sequence that provides resistance to CLA [61].

**Urea breath noninvasive test**

The UBT is extremely believable for detection of H. pylori but for young children the test is more complicated; whereas Canadian consensus guidelines regarded 13C-UBT to be the most excellent noninvasive test for the detection of H. pylori infection in children [45]. Studies have shown that UBT is the best option for H. pylori infection treatment which is completed eradication therapy after four to 6 weeks, but for these test proton pump inhibitors administration must be stopped before 2 weeks [62]. This method is used for hydrolysis of urea by H. pylori to produce carbon dioxide and ammonia which are used to detect in breath samples, representing the presence of active H. pylori infection. UBT has a sensitivity and specificity ranging from 88%–95% and 95%–100%, respectively [63].

![Fig. 6: Positive and negative results of Campylobacter-like organism test (CLO) test for Helicobacter pylori. The urease of Helicobacter pylori hydrolyzes urea to release ammonia, which is detected colorimetrically [58]](image)

![Fig. 7: The urea breath test detects urease activity, a marker of Helicobacter pylori infection, through the oral administration of carbon 13-labeled urea. If the stomach is infected with H. pylori, its urease splits the carbon 13-labeled urea to produce ammonia and carbon 13-labeled CO$_2$, which is expired in the breath [64]](image)
Recent studies have shown that 13-labeled UBT (13C-UBT) is a most reliable test for detection of *H. pylori* infection due to rapid, simple, innocuous, easy to repeat, reproducible, highly accurate, and economical manner [7]. Researchers have proved that this test is regarded as the gold standard, highest sensitivity and specificity (>95%), inexpensive, and convenient [64]. It was reported that the American College of Gastroenterology authenticated the carbon 13C-UBT as the most consistent test to confirm *H. pylori* eradication (Fig. 7) [65].

**Stool antigen non-invasive test**

At present, studies have shown that this test is obtainable and suitable for small children, as well as this test is cost-effective and need to less apparatus than UBT [61]. It has been reported that this test can be performed mostly in routine laboratories and also used to provide after the end of *H. pylori* infection treatment [45].

**CONCLUSION**

*H. pylori* infection is one of the global problems which are more affected in developing countries than in developed countries, and major risk factors for gastric cancer and PU. Different methods are used to detect *H. pylori* infection such as non-invasive or invasive test. 13C-UBT is more effective than other tests.

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