

ADVANCES IN DIAGNOSIS AND TREATMENT OF *HELICOBACTER PYLORI* INFECTION

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Helicobacter pylori is a Gram-negative motile bacterium causative agent of acute and chronic digestive and extra-digestive human infections. According to different reports worldwide, *H. pylori* symptomatic and asymptomatic infections are a global problem. The statistical investigations show a percentage of 50 for people who are involved in *H. pylori* acute/chronic digestive and/or extra-digestive infections around the world. This review focuses on digestive and extra-digestive diseases caused by *H. pylori*, the related virulence factors, diagnostic techniques including non-invasive and invasive diagnostics and treatment. There is an abundance of diagnostics for detection and identification of *H. pylori*. The availability, cost, and the condition of test performance may differ from place to place. To increase the level of reliability in association with diagnostic tools for detecting *H. pylori*, several techniques must be applied at once as multi-diagnostic technique. Furthermore, there are several pharmacotherapies which can be used for complete eradication of *H. pylori* infection.

Keywords: *Helicobacter pylori*, diagnostic techniques, treatment

Introduction

Helicobacter pylori is a curved motile Gram-negative spiral bacterium, which has been isolated from gastritis patients by Australian scientists Marshall and Warren in 1983. The unipolar flagellum makes the bacterium highly motile for quick movements and attachments to gastric mucosa. According to some studies, *H. pylori* is naturally able to colonize on the surface of gastroduodenal mucosa of human beings, a relationship with a background of near 60,000 years old [1–11].

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H. pylori is an important bacterial infectious agent that causes significant gastrointestinal tract (GIT) and extra-digestive infections worldwide. Infections caused by *H. pylori* are more frequent in overcrowded populations with low hygiene [3, 4, 12, 13].

The recorded reports from different countries show that approximately 50% of people are infected by *H. pylori* around the world. The coverage system relating to high urease activity enables *H. pylori* to survive in acidic condition of stomach. The powerful ureolytic activity of cytoplasmic urease produced by *H. pylori* catalyses the conversion of gastric juice urea into alkaline ammonia and carbon dioxide which is produced in stomach [5–7, 14–22].

The majority of patients with *H. pylori* GIT infections have no significant clinical gastric involvement and sometimes there are asymptomatic patients. However, chronic gastric inflammation or gastritis is the predominant clinical symptom in association with *H. pylori* digestive infections and it is known as a risk factor in patients with GIT diseases including gastric mucosa in association with lymphoid tissue (MALT) lymphoma, gastric cancer (GC) and adenocarcinoma, gastroesophageal reflux disease, and duodenal ulcers (DU). Complete eradication of *H. pylori* by antibiotics may lead to definitive treatment of early MALT lymphoma. Previous studies indicate a close association between infections caused by *H. pylori* and GC [5, 6, 19, 21, 23–32].

Mostly, people acquire digestive and extra-digestive *H. pylori* infections in their childhood and without any antibiotic therapy they may be carried in an individual's whole life [29].

There are many extra-digestive diseases and infections including autoimmune diseases, bronchiectasis, cardiovascular diseases, colonic and pancreatic diseases, diabetes mellitus, hepatobiliary system diseases, neurological diseases, skin diseases, and hematological diseases that are in association with *H. pylori* (Table I) [13, 30, 32–42].

In the present review, we show the digestive and extra-digestive infections and diseases caused by *H. pylori*, the related virulence factors, diagnostic techniques including non-invasive and invasive diagnostics and treatment.

Virulence Factors in Digestive and Extra-digestive Pathogenic Strains of *H. pylori*

Adhesion is the most important factor for colonization of microorganisms. In consequence, colonization of microbial populations including *H. pylori* may lead to translocation of virulence factors from pathogen into host cell and facilitate the persistence of infection. Thus there are several genes that play

Table I. Extra-digestive diseases and their subgroups caused by *H. pylori*

Extra-digestive group diseases	Subgroups of diseases
Autoimmune diseases	Autoimmune thyroid disease (ATD), Grave's disease, rheumatoid arthritis, Crohn's disease, Behcet's disease
Cardiovascular diseases	Atherosclerotic plaques, ischemic heart disease, Coronary artery disease, stroke
Colonic and pancreatic diseases	Colorectal cancer, colorectal adenoma, colorectal adenocarcinoma, GC
Hepatobiliary system diseases	Non-alcoholic fatty liver disease, cirrhosis, hepatic encephalopathy, liver fibrosis, hepatocellular carcinoma, cholangiocarcinoma
Neurological diseases	Dementia, Alzheimer disease, multiple sclerosis, neuromyelitis optica
Skin diseases	Chronic urticaria, chronic facial dermatosis (rosacea), psoriasis vulgaris, Henoch-Schönlein purpura, alopecia areata, Sweet's syndrome
Hematological diseases	Iron deficiency anemia, pan gastritis, idiopathic thrombocytopenic purpura (ITP)

important role as virulence factors in different pathogenic strains of *H. pylori* (Table II) [21, 30, 43–52].

Genetic studies have corroborated the presence of *cag* pathogenicity island (*cag* PAI) in the pathogenic strains of *H. pylori*. The *cag* PAI is a 40,000 bp chromosomal DNA segment which is made up of 31 genes and divided into *cag* I and *cag* II [21, 30, 47, 53–55].

The pathogenic strains of *H. pylori* causing digestive and extra-digestive diseases encompass *cag* PAI. Therefore, *H. pylori* bacteria are divided into two groups of *cagA*-positive and *cagA*-negative strains. The *cagE* has intensive correlation with *cagA* and both genes contribute in digestive and extra-digestive diseases [21, 30, 56–61].

The *vacA* gene is detected in all strains of *H. pylori* and three alleles including s (signal), i (intermediate), and m (middle) are recognized for it. The *vacA* gene is responsible for longevity of *H. pylori* infection [21, 30, 47–50, 61].

The *dupA*, the DU promoting gene placed in malleability part of the genome of *H. pylori* is known as a bipartite sequence consisted of two genes of *jhp0917* and *jhp0918*.

The *iceA* gene is induced by contact with epithelium possesses the allelic variants of *iceA1* and *iceA2*. The *iceA1* and *nlaIIIIR* (a gene detected in *Neisseria lactamica* encoding a type of restricted enzyme which act in CTAG specific sequence) genes have an ambient homology with each other. The activity of *iceA2* is unknown [30, 61].

The *bab* alleles involving *babA1*, *babA2*, and *babB* are known as blood group antigen binding genes. The *babA2* may be expressed with *cagA* and *vacA* genes and among its alleles, e.g., *babA1* and *babB* have a key role in pathogenesis [30, 62].

Table II. The relationship between virulence factor genes, their functions, and phenotypic manifestations

Genes	Protein	Properties	Function	Phenotypic manifestations
<i>cagA</i>	CagA	Oncoprotein	Formation of bacterial type IV secretion system, Triggering IL-6 production	Gastric inflammation-associated diseases (GIAD), peptic ulcer diseases (PUD), GC, cardiovascular disease, ATD, ITP, hepatobiliary system diseases, colonic and pancreatic diseases
<i>cagE</i>	CagE	Cytokine inducer	Triggering IL-1 β and IL-8 production	PUD, hepatobiliary system diseases
<i>vacA</i>	VacA	Vacuolating cytotoxin	Epithelial cell vacuolation, induction of channels in cell membrane, release of mitochondrial cytochrome c, suppressing T-cell responses	GIAD, PUD, GC, hepatobiliary system diseases
<i>dupA</i>	DupA	Duodenal ulcer promoting gene	Formation of bacterial type IV secretion system, triggering IL-8 production	GC, dyspepsia, PUD such as DU
<i>iceA</i> (<i>iceA1</i> , <i>iceA2</i>)	IceA	Producing via bacterial contact with gastric epithelial cells	Triggering IL-8 production	Asymptomatic gastritis, dyspepsia, PUD such as DU, GC, hepatobiliary system diseases
<i>bab</i> (<i>babA1</i> , <i>babA2</i> , <i>babB</i>)	BabA1, BabA2, BabB	Adhesin	Binding activity to blood group antigens (<i>H. pylori</i> tropism mechanism)	PUD such as DU, intestinal metaplasia, hepatobiliary system diseases, GC
<i>sabA</i>	SabA	Adhesin	Binding to sialylated glycans on the surface of host epithelial and red blood cells, inducing phagocytosis	GIAD, GC
<i>oipA</i>	OipA/ HopH	Pro-inflammatory outer membrane protein	Triggering IL-8 production	GIAD, PUD such as DU

The *sabA*, a sialic acid binding adhesion gene has an effective role in adherence of *H. pylori* to the host cells [30].

The *oipA*, the gene of outer inflammatory protein has a strong correlation with other virulent genes including *cagA*, *iceA*, and *vacA*. *oipA* is an active gene in *H. pylori* pathogenesis [30].

Table III. The relationship among host predisposing factor, type of predisposing factor, and phenotypic demonstration

Host predisposing factors	Type of predisposing factor	Phenotypic demonstration
Gene polymorphism	Polymorphic antagonist genes of interleukin-1 β (IL-1 β) and IL-1 receptors	Raising the progression of GC up to 2–3 times
	Polymorphic regulator genes of tumor necrosis factor- α and IL-8, IL-16	Raising the progression of GC significantly
	Polymorphic receptors belonging to the innate immune system	

The sextette genes including *babA*, *babB*, *hopZ*, *oipA*, *sabA*, and *sabB* encode for the outer membrane proteins that are closely correlated with gastroduodenal lesions and infections via bacterial adhesion. The aforementioned genes are variable in different strains of *H. pylori* [21, 43, 63–65].

Furthermore, enzymes including catalase, lipase, phospholipase, protease, and urease are influent virulence factors in the pathogenesis of *H. pylori* strains [38].

In addition to *H. pylori* virulence factors, there are several genetic factors in human hosts that predispose the digestive and extra-digestive infections and diseases (Table III).

Moreover, the environmental predisposing factors including salt, vinegar, alcohol, and smoke trigger the progression of GC [12, 13, 30, 34, 59, 66, 67].

Diagnostic Techniques

There are several available diagnostic procedures which are categorized into two major groups of non-invasive (without endoscopy) and invasive (with endoscopy) tests. The aforementioned tests are used for detecting digestive and extra-digestive infections and diseases caused by pathogenic strains of *H. pylori*; however, the non-invasive tests are more usual for diagnosing extra-digestive diseases [38, 68–72].

All of the tests including non-invasive and invasive are reliable and accurate, but each one has its limitations. Thus, there is a huge lack of single test as Gold Standard and optimal diagnostic technique. The only way to increase reliability of diagnosis is to apply for a multi-diagnostic tool [70, 73–75].

According to recent studies, for improving diagnostic tests and managing treatments, all individuals with DU disease must be checked via clinical tests before antibiotic therapy. Testing program is a proper strategy for diagnosing and

managing *H. pylori* infection [68, 76–79]. In a day-to-day routine diagnostic method for *H. pylori* infection, there are some factors including sensitivity, specificity, experience level of experts, stage of diagnosis (pre-treatment or post-treatment stages), technical availability, and costs which are considered to employ a particular test [70, 71, 80].

Non-invasive diagnostic tests

Non-invasive assays or non-endoscopic tests are more acceptable and pleasant to individuals; because these tests are cheaper and more comfort and safer in compare with invasive or endoscopic methods. Furthermore, non-invasive techniques are often known as the best choice in epidemiological investigations. Totally, non-endoscopic techniques are recommended for most of the patients with particular situation such as children, pregnant women, and others with any risky condition are recommended for non-invasive diagnostic tools [70, 81–83].

Non-invasive tests are categorized into two main groups of direct and indirect techniques. Stool assay is a direct non-invasive test in which the presence of bacterial antigens is directly evaluated. The assessment of the presence of antibodies or other elements like CO₂ due to *H. pylori* infection is classified as indirect non-invasive techniques including 13C-urea breath test (UBT). The most common non-invasive screening settings of *H. pylori* infection involve UBT and serologic assays. In addition, other reliable tests including stool assay and commercial diagnostic kits are available. However, there are some advantages and disadvantages with each one of the mentioned tools [68, 71, 74, 82].

Non-invasive indirect tests

Ureolytic-based tests

13C-urea breath technique. UBT as a direct non-invasive test with diagnostic accuracy of >95% (sensitivity >95%, specificity >95%) is easy to perform and based on urea hydrolysis achieving within gastric mucosal epithelial cells produces ammonia and CO₂. In this test, when an individual with *H. pylori* infection ingests 13C-labeled urea, *H. pylori* as a famous urease enzyme producer breaks down the urea and the labeled CO₂ will be monitored within a short time. It takes 2 h for collecting the breath samples of patients. Also, a single sample is collectible in 40 min by the help of hyamine as a CO₂ trapping agent for exhaling into it. Finally, the percentage of radioactivity of each sample is calculated by a scintillation counter. 13C has a non-radioactive property; so, the test is safe for children and pregnant women. UBT is occurred in different manners such as meal-based 13C UBT, tablet-based 13C UBT, and 14C UBT. Recently, the tablet-based

¹³C UBT is recommended. Different reports confirm UBT as an accessible, accurate, safe, and practical test [70, 73, 83–87].

Serum bicarbonate and ammonia vapor tests. In addition to UBT, there are other ureolytic techniques including serum bicarbonate and ammonia vapor which have their special applications. In serum bicarbonate test, the measure of serum ¹³C-carbonate is evaluated. This test is reliable and suitable as post-treatment setting.

Ammonia vapor test is used for assessing the level of ammonia gas in the patient breath. This method is absolutely cost effective method [71–88].

Immunologic techniques

Serological tests. Serological tests are divided into four formats including the enzyme-linked immunosorbent assay (ELISA), agglutination, western blotting, and immunochromatography [70, 71, 89].

Serological tests regarding *H. pylori* infection diagnosis are designed for detecting specific antibodies such as anti-*H. pylori* IgG antibodies or anti-CagA and anti-VacA antibodies. In adults, the preferable sample is serum, while in children is saliva or urine. Serologic diagnostic tools are cheap with high limitations. However, the serological tests are common and accessible in a wide range. Depending on the type of serological tests, their sensitivity is up to 90%–97% and the specificity of them varies from 50% to 96%. Thus, each serological test must be used in validated settings. Some of the serological commercial kits are suitable and available [68, 70, 71, 73, 90].

Serological tests are not capable to distinguish active infection from previous contact. Today, serological tests are the third common techniques between non-invasive tools for diagnosing *H. pylori* infection. According to previous reports, the use of combined serological methods may increase the sensitivity and the specificity of the tests [70, 71, 73, 90, 91].

Salivary and urinary tests. For decreasing the stressful condition of venepuncture in children, serum test is replaced by saliva or urine tests in children. In comparison with sera samples, the results of salivary antibody assays demonstrated inappropriate sensitivity and specificity; but it seems that the use of special applicators as beneficial device increases the sensitivity and the specificity of the tests [70, 71, 92–95]. Some reports show the preference of urine assay with higher sensitivity and specificity [71, 96, 97].

Near-patient assays. The near-patient assays seem to be an on-site and fast technique with low sensitivity and specificity. Totally, the accuracy of near patient assays is low. The final results vary depending on the condition of whole blood. The whole blood taken from capillary system show different results (sensitivity and specificity) than the venous whole blood because of their various components'

concentrations. Therefore, the near-patient assays are not recommended when the laboratory-based tests are available [70, 71].

Non-invasive direct tests

Stool antigen test (SAT). The SAT or fecal antigen test (FAT) is known as rapid, simple, and facilitated technique which is based on fecal antigen detection of *H. pylori*. In new format of the SAT or FAT, polyclonal antibodies are replaced by monoclonal antibodies. The SAT or FAT is divided into two forms of laboratory tests (e.g., ELISA with high accuracy) and speedy in-office tests (e.g., immunochromatographic method with limited accuracy). According to previous reports, the sensitivity as well as the specificity of the SAT or the FAT is ~95%. The SAT or the FAT assays are useful for pre-treatment and posttreatment diagnosis of *H. pylori* infection. The SAT or the FAT tests are improved the level of diagnostics of *H. pylori* infection. Among non-invasive diagnostic techniques, for pre-treatment diagnosis of *H. pylori* infection, the UBT and the SAT (FAT) tests have the same value in accuracy; but for posttreatment diagnosis of *H. pylori* infection, the UBT is the first choice and the SAT (FAT) is the second one [4, 68, 70, 71, 86, 98–102].

Invasive diagnostic tests

Invasive tests or endoscopic techniques based on biopsy (histology), culture, rapid urease test (RUT), molecular biology, e.g., polymerase chain reaction (PCR) are used for detecting *H. pylori* infection, worldwide. The situation of patients determines the type of invasive tests. An appropriate specimen raises the accuracy of the test [5, 70, 83, 86].

Urease-based assays. Urease tests such as RUT are rapid, cheap with proper accuracy but they have to be validated for different groups of the patients. *H. pylori* is a typical bacterium, which produces a huge amount of urease enzymes. The biopsy specimen is laid into a buffer free urea solution with a pH indicator of phenol red. The presence of *H. pylori* in the biopsy may lead to conversion of urea into ammonia and carbon dioxide which in consequence, the pH raises up and the color of solution start to change. The sensitivity of RUT is ~95% and the specificity depending on its performance varies from 85% to 95% [4, 5, 68, 70].

Histologic-based assays. Histologic techniques indicate a proper evidence of illustrated information through providing sections from gastric mucosa infected by *H. pylori*. The presence of *H. pylori* is distinguished via typical curved appearance of the microorganism on the gastric epithelial cells. The biopsy specimens are stained by different stains including Warthin–Starry silver stain, Giemsa, Genta,

alcian yellow-toluidine blue, immunochemical stains, and hematoxylin and eosin. The Giemsa stain is more common and it has a sensitivity of 90%. Genta's stain gives a qualified illustration of *H. pylori* and the tissue. The alcian yellow-toluidine blue is a proper stain with the same sensitivity as Giemsa stain. But the former is cheap, facilitated, and gives qualified contrast.

Immunochemical stains with monoclonal antibodies increase the specificity of the histologic tests [5, 70, 103–105].

It is important to know that the specificity of histologic-based tests is >95% while the sensitivity of these tests relying on quality of the biopsy, location of biopsy, size of the biopsy, frequency of the biopsy, and the applied staining varies from 50% to 95% [68, 70].

Culture-based assays and antimicrobial susceptibility tests. In the most cases, culture tests are used for antibiotic therapy and their applications for clinical diagnostics are rare. Biopsies containing *H. pylori* must be cultured in the minimum time; because *H. pylori* is very sensitive to environmental factors. The Stuart's transport medium is a suitable choice to recover the bacteria within 24 h at 4 °C. Mostly biopsies are used for culture media, but oral or fecal specimens may be used rarely. The culture medium of Brain Heart Infusion Agar base comprising blood, starch, charcoal, and bovine serum albumin is used for culture-based tests [68, 70, 86].

The culture-based tests are mainly used for sensitivity testing of *H. pylori*. The antimicrobial susceptibility tests reveal suitable antibiotics for infection treatment and show the pharmacological resistances. An accurate test may lead to a definite and proper treatment. The common antibiotics which are used for treatment involve amoxicillin, clarithromycin, metronidazole, and tetracycline. Some resistant strains are reported for metronidazole and clarithromycin. Depending on the number of biopsies, culture medium, transport style, and methodology, the sensitivity of culture-based assays varies from 50% to 95% while the specificity of these techniques is >95% [68, 70, 86, 106].

Molecular biology tests. Molecular biology techniques have a vast range of application from diagnosing to typing. Also, samples may be taken either from cultures or from specimens. Different types of molecular techniques including *in situ* hybridization, PCR, multiplex-PCR, real-time PCR and DNA microarray can be used in clinical diagnostics. The sensitivity and the specificity of molecular tools are >95%. Molecular biology tests are often used for identification of antibiotic resistant strains. Among aforementioned molecular diagnostics, DNA microarray is an advanced accurate and rapid diagnostic technique which can be used when there are a huge number of clinical samples. DNA microarray is a powerful technique for detection and identification of drug-resistant and susceptible microbial strains. However, this technique is expensive when the number of clinical specimens is low [70, 86, 107–116].

Fluorescent in situ hybridization (FISH). FISH is an accurate, rapid, reliable, sensitive, and specific molecular diagnostic method based on targeting the *H. pylori* 16S rRNA and 23S rRNA genes by fluorescein-labeled oligonucleotide probes. According to previous investigations, FISH is an advanced diagnostic technique with high sensitivity (97%) and specificity (94%). Furthermore, this method is able to recognize antimicrobial resistant bacteria and in particular clarithromycin-resistant strains of *H. pylori*. The recognition of clarithromycin-resistant and clarithromycin-susceptible strains of *H. pylori* takes only 3 h. However, FISH costs expensive and is not suitable for children and young adults. Until now PCR techniques and in particular real-time PCR are routine clinical methods for detection and identification of drug-resistant and susceptible strains of *H. pylori*; moreover, real-time PCR is easy to achieve, rapid, with high sensitivity (98%) and specificity (92%). It is also a cost effective technique [117–124].

In recent years, a new developed technique has raised up which is based on FISH and can be performed in the form of *in vivo*. The method of fluorescence *in vivo* hybridization (FIVH) is a combined technique consisted of confocal laser microscopy, FISH, and histopathological assays. The preference of this diagnostic technique is the ability of direct observation of live fluorescent *H. pylori* cells as motile and non-motile bacterial cells within mucosal tissues and gastric epithelial cells, respectively. The real time technique of FIVH is an appropriate diagnostic tool for detecting and identifying different type of bacterial cells including *H. pylori*. There are some limitations for utilizing FIVH as a routine clinical diagnostic tool. Using special parts of the body, the level of pH, the need of confocal laser endomicroscope, and high costs are important limitations for application of FIVH as a routine clinical method. However, there is promising future for FIVH by omitting the aforementioned limitations [121, 125, 126].

Treatment of *H. pylori* Infection

There are several pharmaceutical regimens which are used for treating digestive and extra-digestive *H. pylori* infections and diseases. Rapid and accurate diagnosis has an important role for treatment and eradication of *H. pylori*. Because of particular localization of *H. pylori* in gastric mucus layer, there is a need of effective pharmacotherapy. The drugs must be penetrated into gastric mucosal layer to prevent colonization of *H. pylori*. Therefore, monotherapy is not a good choice for complete eradication of *H. pylori*. Even dual therapy is not sharp effective. Mostly, triple treatment including two antimicrobial agents (antibiotics) with a proton-pump inhibitor (PPI) (antisecretory agent) or a bismuth salt is administered. However, quadruple therapy in which two antibiotics, combined

with a PPI and a bismuth salt is sometimes a suitable alternative for complete treatment of *H. pylori* infection. There are some antibiotics such as clarithromycin, tetracycline, metronidazole, and amoxicillin that have acceptable pure rate for eradication of *H. pylori*. Metronidazole is a proper replacement for amoxicillin in patients that have penicillin allergy. The role of PPIs is to block the H⁺, K⁺ ATPase pump and the bismuth salts have lytic effect on *H. pylori* by disrupting the bacterial cell wall. The effects of dual, triple, and quadruple therapies are 70%, 85%, and 66.7%, respectively. Besides, the side effects of quadruple therapy are more than the other therapies. However, it is an alternative for treatment-resistant strains of *H. pylori* which cause to triple therapy failure [4, 5, 38, 86, 127, 128].

In accordance with a wide range of studies, the prevalence of drug-resistant strains of *H. pylori* is clearly different from a region to another geographic area. But the results indicate a remarkable increase in association with drug resistance rate in many countries. Among a diversity of antibiotics, a significant increase of resistance rate against clarithromycin, levofloxacin, moxifloxacin, and metronidazole has been recognized between *H. pylori* strains. Some reports show the incredible increase of clarithromycin and metronidazole resistance rates up to 80%. On the other hand, the tetracycline and amoxicillin resistance rates are low and insignificant in the majority of geographic areas, but not in Africa. These reports emphasize the increase of pharmacotherapy failures which is related to high general usage of antibiotics around the world. As the drug resistance rates vary from a country to another, a local pharmacotherapy may be a good solution for decreasing the rate of antimicrobial resistance among the strains of *H. pylori* [122, 129–133].

Conclusion

H. pylori is one of the most important bacteria which may lead to different forms of acute and chronic digestive and extra-digestive infections and diseases. There are several virulence factors that support the level of bacterial pathogenicity. Simultaneously, risk factors in susceptible people may accelerate the progression of *H. pylori* infection. It is important that people with gastrointestinal disorders with or without extra-digestive diseases must be checked and be controlled with intervals.

Always the practical prophylactic health care is the first choice in the field of infectious diseases. Rapid and accurate diagnostics are absolutely determinant factors to control and treat the infection in early stages.

There are various invasive and non-invasive diagnostic methods for detecting *H. pylori* infections and diseases.

Among non-invasive assays UBT and SAT (FAT) are first-line diagnostic approaches and the serological tests have the low accuracy. However, the availability, cost, and the condition of test performance may differ from place to place. Thus, to improve the diagnostic methods there is no choice rather than combination of two or more techniques with each other.

There are a number of pharmacotherapies, depending on the condition of infections and diseases. Preferably, triple therapy is an appropriate choice but in the presence of drug-resistant strains, quadruple therapy is recommended.

Conflict of Interest

The authors declare no conflict of interest.

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