MINI REVIEW

PEPTIC ULCER DISEASE: PATHOGENESIS AND DIAGNOSIS

Zubair Anwar1,*, Qurat E Noor Baig1, Aqeela Khurshid2, Adeela Khurshid2, Iqbal Ahmad1
1 Baqai Institute of Pharmaceutical Sciences, Baqai Medical University, Karachi, Pakistan.
2 Faculty of Pharmacy, Jinnah University for Women, 5C, Nazimabad, Karachi, Pakistan.

ABSTRACT
Helicobacter pylori is a gram-negative bacteria which forms colonies in gastric mucosa and is responsible for peptic ulcer diseases (PUDs). The present review deals with the strategies employed in the diagnosis of H. Pylori infection. The diagnostic techniques for H. pylori infection are categorized into invasive and non-invasive. The invasive techniques include endoscopy, histological studies, culture and rapid urease test whereas 13C-urea breath test, stool antigen test, blood test, serology and PCR are included in non-invasive techniques. A brief outline of these techniques with their selection criteria has been discussed in this review.

Keywords: Peptic ulcer disease, Helicobacter pylori, diagnosis, invasive techniques, non-invasive techniques.

1. INTRODUCTION
Peptic ulcer disease (PUD) has been considered as a prime cause for the entire world due to its morbidity and mortality1. PUD is erosion in the lining of stomach or first part of small intestine, commonly known as duodenum2. These linings have a protective sheath of mucus that prevents the acid contact. The impairment of the mucus lining leads to sores or lesions3. The major symptoms of PUD include epigastric pain associated with dyspepsia, nausea, pyrosis or regurgitation, unintended weight loss, recurrent vomiting, anemia, dysphagia, odynophagia and bleeding4-6. Helicobacter pylori (micro-acrophilic spiral bacillus) bacteria are considered the predominant causative agent for the pathogenesis of peptic ulcer7-9.

2. PATHOGENESIS OF PUD
Impaired mucosal defense mechanism and gastric acid hypersecretion are the significant factors vulnerable to the prognosis of PUD. Chronic gastritis, gastric metaplasia, impaired alkalinization in the duodenum and gastric atrophy are the characteristic features of peptic ulcer10.

3. THERAPEUTIC MANAGEMENT OF PUD
The eradication of H. pylori is a pre-requisite for healing of peptic ulcer as it is one of the strongest risk factor. Strategies are included to bring down the acid secretions by using acid suppressants, proton pump inhibitors, H2 receptor antagonists and anti H. pylori drugs11-13.

4. DIAGNOSTIC STRATEGIES
4.1. Classification of Diagnostic Methods
Since H. pylori is a notable causative agent of peptic ulcer, most of the common diagnostic techniques are based on the detection of presence or absence of the bacterium. Diagnostic techniques for the detection of H. pylori have been classified into invasive and non-invasive methods14. In invasive methods, H. pylori is determined by direct analysis of gastric biopsy samples (e.g. endoscopy, histological studies, culture, rapid urease test) whereas in non-invasive methods H. pylori is determined by the analysis of a variety of test samples resulting in the indirect identification of the bacterium (e.g. 13C-urea breath test, stool antigen test, blood test, serology, PCR)14,15.

4.2. Selection of Appropriate Test
A diagnostic test should be selected on the basis of following criteria15:

a) Appropriate accuracy, specificity, sensitivity and precision of the test.
b) Clinical manifestation of alarming signs.
c) Cost-effectiveness of the applied technique.

* Corresponding Author Email: zubair_ana@hotmail.com
4.3. Invasive Techniques

4.3.1. Endoscopy
Collection of a tissue sample (i.e. biopsy) from the stomach lining is one of the most reliable methods for the detection of *H. pylori* infection. Endoscopy aids in visualizing the deformities like gastritis, hemorrhage and early diagnosis of polyps and tumors. However, it is an expensive, time consuming and rather unpleasant method for the detection of *H. pylori*. In terms of accuracy, it is one of the reliable strategies for the diagnosis of benign or malignant gastric ulcers.

4.3.2. Histology
Inflammation and presence of bacterium can be diagnosed through histological examination. The detection of *H. pylori* can be achieved with high sensitivity and low cost by using Giemsa, hematoxylin and eosin (H & E), Genta, Warthin-Starry silver, and / or immunohistochemical (IHC) staining. It is recommended to use a combination of staining techniques for the identification and diagnosis of *H. pylori*. H & E and Giemsa staining are reported to have advantage over other stains because of their simplicity and consistency.

4.3.3. Culture
The specimens collected from biopsy are applied over Columbia blood agar plate by using 35°C temperature for incubation. After 4 to 5 days, the culture of *Helicobacter* is considered to be positive if morphological examination shows spiral or curved bacilli as well as appearance of gram negative activity and positive results for oxidase, catalase and urease.

4.3.4. Rapid urease test
This test is also known as Campylobacter like organism (CLO) test. This test is rapid and easy to perform with low cost and acceptable specificity and sensitivity. This test is based on the detection of urease enzyme, which is released in large quantity by *H. pylori* and is responsible for the breakdown of urea into ammonia and CO₂. The solution turns red from yellow in 24 hours if the gastric specimen is positive.

4.4. Non-Invasive Techniques

4.4.1. ¹³C urea breath test
In this test, 75 mg of ¹³C-labelled urea tablets are administered to the patients. The test exploits the hydrolysis of urea into ammonia and ¹³CO₂. The labeling of urea with ¹³C, which is a non-radioactive isotope of ¹²C, is safe in both women and children and can be repeated for multiple times in a single patient. The breath samples are taken at different time intervals and are analyzed using infrared or mass spectrometry or any other suitable technique for ¹³CO₂. The ¹³C-labelled urea tablets may also contain citric acid, which is known to play a role in the recovery of ¹³CO₂.

4.4.2. Stool antigen test
Examination of patient’s stool for the detection of *H. pylori* antigen is another useful technique of diagnosis. Two different types of test kits are used i.e. monoclonal antibody and polyclonal antibody. The type of antigen selected for the detection greatly affects the test efficiency and accuracy.

4.4.3. Blood test
Blood test is performed in order to measure the antibodies to *H. pylori* in the serum. The major drawback of this test is that it does not confirm whether the infection is new or old and it remains positive for years even if the infection has been cured.

4.4.4. Serological tests
Serological tests detect specific IgG and IgA antibodies in the serum prepared against *H. pylori*. A number of different serological tests are in practice which includes ELISA, latex agglutination and western blotting methods. The later is of utmost importance as it constitutes the maximum accuracy, low cost and fast pace in the analysis. Like blood tests, serology is not performed for the confirmation of eradication of *H. pylori* infection.
4.4.5. Polymerase chain reaction (PCR)
A wide range of clinical specimens (gastric biopsy, feces, urine, saliva) are obtained to check the presence of bacterium through PCR using specific primers which is known to be a highly sensitive technique for the detection of H. pylori infection\textsuperscript{22}.

4.5. Application of Combination Techniques
No test can prove to be the ideal in investigating the bacterial infection alone. Kalach et al.\textsuperscript{23} revealed in their studies that the status of H. pylori can be considered as positive when two of the three tests (histology, rapid urease test and culture) show same results otherwise it would be considered as negative.

4.6. Recent Advancement in Diagnostic Strategies
The $^{14}$C-urea breath test has made its place in developing countries because of the ease in performance, reliable outcomes and higher sensitivity. It is considered to be simpler than $^{13}$C urea breath test excluding the use of mass spectrometer for detection. However, patients are exposed to less harmful radiations during the 24 hours period. Another novel technique, i.e. rapid stool antigen test based on lateral flow immunoassay, made its way in routine clinical practices because of least possible utilization of laboratory equipments, reduced cost and minimal skills required in performing the test. This is one of the rapid test providing results in just a span of 5 minutes\textsuperscript{24}.

5. CONCLUSION
H. pylori is a persistent colonizer of human stomach and is responsible for PUD. It has been categorized as group 1 carcinogen by World Health Organization (WHO). A number of antibiotics are effective in the treatment of H. pylori infection. However, it is of utmost importance that correct diagnosis should be made on time. A number of techniques are available for the diagnosis of H. pylori. Although use of multiple tests is recommended for the diagnosis of H. pylori infection but the decision totally relies on the judgment and maturity of the physician.

REFERENCES