

Full length Research paper

Peptic ulcer and *Helicobacter pylori* eradication: A review article

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***Helicobacter pylori* infection with relation to peptic ulcer disease has been the subject of exhaustive research. It is widely accepted that *H. pylori* is the major cause of peptic ulcer disease. In Pakistan, infection rate was about 83% in adult patients undergoing upper gastrointestinal endoscopy for various reasons. Infection with *H. pylori* is associated with a three to six fold increase in the risk of developing non cardiac (body and antrum) stomach cancer. The bacterium *H. pylori* can infect the stomach during child hood and cause life long chronic gastritis, which can lead to peptic ulcer disease and since reinfection in adults is extremely rare, adequate treatment permanently cures this former chronic recurrent, serious disease. If ulcers do not recur neither do ulcer perforation nor bleeding; then quality of life increases. Antibiotic resistance needs to be taken into account when designing treatment for *H. pylori* infection. Over the past decade, many different therapies were recommended and prescribed that resulted in inhibiting the malaise onset of *H. pylori* change rapidly. Eradication of *H. pylori* has been demonstrated to be useful for preventing the relapse of gastric and duodenal ulcer. In this article, we try to provide a basic frame work on which diagnosis and treatment modalities can be based for its curative and preventive function.**

Key words: *Helicobacter pylori*, ulcer disease, treatment.

INTRODUCTION

Helicobacter pylori is the major cause of gastro duodenal disease like peptic ulcer and important risk factor for gastric carcinoma and primary gastric lymphoma. *H. pylori* cause more than 90% of duodenal ulcers and up to 80% of gastric ulcers. *H. pylori* is a spiral shaped bacterium that was first confirmed to be present on the gastric surface in the 1983. When this bacterium was discovered, spicy food, acid, stress, and lifestyle were considered to be the major causes of ulcers. The majority

of patients were given long term medications, such as H2 blockers, and more recently, proton pump inhibitors, without a chance for permanent cure. These medications relieve ulcer related symptoms, heal gastric mucosal inflammation, and may heal the ulcer, but they do not treat the infection. When acid suppression is removed, the majority of ulcers, particularly those caused by *H. pylori*, recur. Since it is known that most ulcers are caused by *H. pylori*, appropriate antibiotic regimens can successfully eradicate the infection in most patients, with complete resolution of mucosal inflammation and a minimal chance for recurrence of ulcers (Marshall and Warren, 1983).

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Diagnostic testing

Currently, there are several popular methods for detecting the presence of *H. pylori* infection, each having its own advantages, disadvantages and limitations. Basically, the tests available for diagnosis can be differentiated according to whether or not endoscopic biopsy is necessary. Histological evaluation, culture, polymerase chain reaction (PCR), and rapid urease tests are typically performed on tissue obtained at endoscopy. Alternatively, simple breath tests, serology, and stool assays are sometimes used, and trials investigating PCR amplification of saliva, feces, and dental plaque to detect the presence of *H. pylori* are ongoing (Ananthakrishnan and Kate, 1998).

Histology

Histological evaluation has traditionally been the gold standard method for diagnosing *H. pylori* infection. The disadvantage of this technique is the need for endoscopy to obtain tissue. Limitations also arise at times because of an inadequate number of biopsy specimens obtained or failure to obtain specimens from different areas of the stomach. In some cases, different staining techniques may be necessary, which can involve longer processing times and higher costs. However, histological sampling does allow for definitive diagnosis of infection, as well as of the degree of inflammation or metaplasia and the presence or absence of MALT lymphoma or other gastric cancers in high risk patients (Malfertheiner et al., 2007).

Culture

However, because *H. pylori* is difficult to grow on culture media, the role of culture in the diagnosis of the infection is limited mostly to research and epidemiologic considerations. Although this culture is costly, time consuming and labor intensive culture does have a role in antibiotic susceptibility studies and studies of growth factors and metabolism (Fischbach, 2000).

Polymerase chain reaction

With the advent of PCR, many exciting possibilities emerged for diagnosing and identifying *H. pylori* infection. PCR allows the identification of the organism in small samples with few bacteria present and entails no special requirements in processing and transport. Moreover, PCR can be performed rapidly and cost effective, and it can be used to identify different strains of bacteria for pathogenic and epidemiologic studies. The PCR can detect segments of *H. pylori* DNA in the gastric mucosa of previously treated patients, false positive results can

occur, and errors in human interpretation of bands on electrophoretic gels can likewise lead to false negative results (NIH Consensus Conference, 1994).

Rapid urease testing

Rapid urease testing takes advantage of the fact that *H. pylori* is a urease producing organism. Samples obtained on endoscopy are placed in urea containing medium; if urease is present, the urea will be broken down to carbon dioxide and ammonia, with a resultant increase in the pH of the medium and a subsequent color change in the pH dependent indicator. This test has the advantages of being inexpensive, fast, and widely available. It is limited, however, by the possibility of false positive results; decreased urease activity, caused either by recent ingestion of antibiotic agents, bismuth compounds, proton pump inhibitors, or sucralfate or by bile reflux, can contribute to these false positive results (Abraham and Bhatia, 1997).

Urea breath test

A urea breath test similarly relies on the urease activity of *H. pylori* to detect the presence of active infection. In this test, a patient with suspected infection ingests either ^{14}C -labeled or ^{13}C -labeled urea; ^{13}C -labeled urea has the advantage of being non radioactive and thus safer (theoretically) for children and women of child bearing age. Urease, if present, splits the urea into ammonia and isotope-labeled carbon dioxide; the carbon dioxide is absorbed and eventually expired in the breath where it is detected. Besides being excellent for documenting active infection, this test is also valuable for establishing absence of infection after treatment, an important consideration in patients with a history of complicated ulcer disease with bleeding or perforation. In addition, a urea breath test is relatively inexpensive (whichever isotope is used) is easy to perform, and does not require endoscopy. However, if the patient has recently ingested proton pump inhibitors, antibiotic agents, or bismuth compounds, a urea breath test can be of limited value. Moreover, except for major medical centers or tertiary referral centers where results are usually available in fewer than 24 h, a urea breath test may be further limited by a turn around time of several days (or longer) required for transport of samples and analysis by specialized laboratories not present in many community settings (Tandon, 2000).

Serologic tests

In response to *H. pylori* infection, the immune system typically mounts a response through production of

immunoglobulin to organism specific antigens. These antibodies can be detected in serum or whole blood samples easily obtained in a physician's office. The presence of IgG antibodies to *H. pylori* can be detected by use of a biochemical assay, and many different ones are available. Serologic tests offer a fast, easy, and relatively inexpensive means of identifying patients who have been infected with the organism. However, this method is not a useful means of confirming the eradication of *H. pylori*; several different samples and changes in titers of specified amounts over time would be needed. In addition, few patients become truly seronegative, even after eradication of the organism. In low prevalence populations, serologic tests should be a second-line methodology because of low positive predictive value and a tendency toward false positive results. Serologic tests may be useful in identifying certain strains of more virulent *H. pylori* by detecting antibodies to virulence factors associated with more severe disease and complicated ulcers, gastric cancer, and lymphoma (Chiba et al., 1992).

Stool antigen testing

Stool antigen testing is a methodology that uses an enzyme immunoassay to detect the presence of *H. pylori* antigen in stool specimens. There is a cost effective and reliable means of diagnosing active infection and confirming cure, such testing has a sensitivity and specificity compared to those of other noninvasive tests (Peterson et al., 1993).

General diagnostic principles

The question of, which patients to test, when to test them, and what test to use, still poses problems for many physicians. Ultimately, the answer to these questions must be based on patient preference, cost, availability of different tests, and positive and negative predictive values of different tests (which depend on the individual patient population, including the prevalence of disorders caused by *H. pylori* infection in the community). Nevertheless, certain principles of testing seem universal. First, endoscopic methods of diagnosis should be used only if the procedure is necessary to detect some other condition besides *H. pylori* infection. Second, only those patients in whom treatment will make a difference should be tested. Conclusive evidence does not exist that eradication of the infection in patients with simple dyspepsia will relieve symptoms, and testing of asymptomatic patients without a history of documented peptic ulcer disease is not warranted. Testing can be considered on a case by case basis in patients with symptoms, suggestive of peptic ulcer disease. Because treatment of *H. pylori* infection is definitely indicated in

patients with active or previously documented peptic ulcer disease, gastric MALT lymphoma, or family history of gastric cancer; their *H. pylori* status must be clarified. Urea breath and stool antigen tests are the most cost effective tests to identify active infection, but their limitations must be considered. Serology is an excellent, inexpensive test to ascertain if someone with a history of peptic ulcer disease and unknown *H. pylori* status warrants treatment, thus endoscopy with tissue sampling in patients with a history of peptic ulcer disease can provide more definitive diagnosis of *H. pylori* infection, as well as information about the activity of peptic ulcer disease and possibly other factors at play (including gastric carcinoma). Follow up testing with urea breath or stool antigen tests which have both sensitivities and specificities greater than 90% is necessary to document cure in patients with complicated peptic ulcer disease e.g. perforation, hemorrhage, obstruction or recurrent symptoms and should be performed 4 weeks after completion of treatment (Bardhan et al., 1997).

Management

General treatment principles

Determining the optimum treatment of *H. pylori* infection is difficult because the organism lives in an environment that is not easily accessible to many medications and because emerging bacterial resistance presents an added challenge. Moreover, many of the recommended regimens are difficult for patients to take, leading to problems with compliance; specifically, taking a large number of pills at least twice daily and coping with unpleasant adverse effects that encourage patient cooperation a little. Despite these obstacles, current regimens can obtain cure rates in excess of 85% in most patient populations (De Boer and Titrate, 1995).

Patient management in primary care

The majority of patients infected with *H. pylori* present initially in primary care, suffering from dyspeptic symptoms with or without alarm symptoms. This is where many of them can and should be treated for the infection, even though, in the absence of endoscopy, the primary care physician may not have an accurate diagnosis of the underlying disease pathology. In this environment, primary care physicians need to have a clear understanding of the major role that they play for the treatment of *H. pylori*. The recommendations given here are particularly relevant to the management in primary care, but many of them apply across clinical practice. Two strongly recommended indications that should be noted here as particularly relevant in primary care are patients who are first degree relatives of gastric cancer

patients and eradication therapy in response to patients' wishes after full consultation. As recommended in the original Maastricht Consensus Report, a 'test and treat' approach should be offered to adult patients under the age of 45 years (the age cut-off may vary locally according to the mean age of gastric cancer onset), thereby presenting, with persistent dyspepsia, in primary care. Several studies have since been published that support this recommendation (Anantharishanan and Kate, 1997).

Antibiotic agents

Currently, antibiotic agents used to treat *H. pylori* infection are administered in combination, while no single agent ever used as monotherapy, due to lack of efficacy and the potential development of resistance. Metronidazole or likewise proton pump inhibitor has activity that is independent of pH, but resistance to the drug is common in many parts of the world. This problem with resistance is ameliorated somewhat, however, when the drug is used with clarithromycin. Metronidazole can have unpleasant adverse effects (e.g. nausea) and a disulfiram-like reaction to alcohol ingestion is possible, although exceedingly rare. Clarithromycin has lower rates of resistance (approximately 7 to 11%), but is not acid stable, may cause dysgeusia and is more expensive than other antibiotic agents. Resistance to amoxicillin is rare, but this drug usually requires the co-administration of a proton pump inhibitor because its activity is pH-dependent. Finally, tetracycline has the advantage of low cost and low occurrence of resistance, but can cause discoloration of the teeth in children and photosensitivity reactions (Marshall et al., 1987).

Adjunctive agents

The most popular agents currently used in combination with antibiotic agents to eradicate *H. pylori* infection are the proton pump inhibitors, that is, omeprazole or like wise proton pump inhibitor being the most widely studied drug. Omeprazole acts not only by directly inhibiting bacterial microsomal enzymes, but also by raising intra-gastric pH, thus facilitating the action of antibiotic agents, reducing gastric secretions, and increasing antibiotic concentrations in the stomach. Other adjunctive agents include histamine receptor antagonists and ranitidine bismuth citrate, which has anti secretory properties in addition to the antibacterial action of bismuth (that is, interruption of the bacterial cell wall). Ranitidine bismuth citrate is no longer available (Penston, 1994).

Current regimens

Presently, the most efficacious regimens include two antibiotic agents and at least one adjunctive agent for 14

days. A literature citation study carried out has claimed adequate cure rates with a 7-day course of quadruple therapy (two antibiotics, two adjunctive agents), but other studies have not confirmed this finding. Most clinicians treat *H. pylori* infection with a triple drug or even quadruple-drug approach.

1. Administration of a proton pump inhibitor, clarithromycin and either metronidazole or amoxicillin for two weeks.
2. Administration of ranitidine bismuth citrate (this guideline preceded the drug's withdrawal in the United States), clarithromycin and either metronidazole, amoxicillin, or tetracycline for two weeks.
3. A proton pump inhibitor, bismuth, metronidazole and tetracycline for two weeks.

For patients who fail initial triple-drug therapy, according to follow-up testing, subsequent therapy should involve using a different combination of available antibiotic agents, increasing the duration of treatment, or incorporating a course of quadruple therapy. Culture with sensitivity testing should be performed after twice treatment failures (Janan et al., 2001).

Antibiotics and other agents

As emerging drug resistance continues to plague efforts to eradicate *H. pylori* infection, new therapeutic regimens incorporating existing antibiotic agents and newly developed compounds are essential. Nitazoxanide is an effective agent when used in combination with omeprazole, and further studies are ongoing. In addition, macrolides other than clarithromycin may play a role in future therapies. The mapping of the complete genome of *H. pylori* has opened the door for a new era in chemotherapeutic drugs. It will now be possible to develop agents that act on specific key protein products that are vital to the survival of the bacterium (Glupezynski and Burette, 1990).

Regimens for *H. pylori*

Many antimicrobial agents have been studied for their efficacy in eradicating *H. pylori* infection either as a single agent or as a combination therapy. However, single antibacterial agent treatment schedules have not been sufficiently effective with eradication rates ranging from only 23% for amoxicillin to 54% for clarithromycin. Single drug regimens are not advocated due to the potential for the development of antibiotic resistance especially to macrolides and nitroimidazoles, which are the key agents in the multidrug regimens for *H. pylori*. Dual treatments combining, a proton pump inhibitor (PPI) with either clarithromycin or amoxicillin was popular a few years ago as they were easy to explain to the patients and

were well tolerated. The newer dual drug regimen of ranitidine bismuth citrate (RBC) and clarithromycin for two weeks has shown few side effects and has a superior eradication rate compared to other dual therapies. However, it has still not been widely evaluated. Overall dual therapies are not very much in current use for the eradication of *H. pylori* due to low eradication rates (Howden and Hunt, 1998).

Gastric ulcer

The main point of difference in the management of a patient with *H. pylori* associated gastric ulcer is the need to exclude malignancy in an apparently benign gastric ulcer. Patients with gastric ulcer should, therefore, be re-endoscope for about 8 weeks after *H. pylori* eradication therapy to confirm healing, obtain further biopsies if eradication of *H. pylori* leads to healing of gastric ulcer and markedly decreases the incidence of relapse. The effect of eradication of *H. pylori* on gastric ulcer complication is unknown at present. Antisecretory maintenance treatment should, therefore, be initiated after successful eradication of *H. pylori* in those patients with gastric ulcer who have a history of hemorrhage or perforation, until complete healing of the ulcer is confirmed at follow up endoscopy (Harris, 1997).

H. pylori and gastric cancer

Infection with *H. pylori* is associated with a three to six fold increase in the risk of developing non cardiac (body and antrum) stomach cancer. Although prevention of gastric cancer through eradication of *H. pylori* is potentially extremely important in global terms (750,000 deaths attributable annually to the neoplasm), it must be emphasized that at present, there is no evidence that eradication of *H. pylori* decreases that risk, nor is it known at what stage *H. pylori* has to be eradicated to prevent the progression of chronic gastritis to atrophy, intestinal metaplasia and eventually to invasive cancer. Although infection with *H. pylori* is very common, the lifetime risk of developing non cardiac stomach cancer in infected individuals in the developed world is estimated to be less than 1%. In subjects with other risk factors for stomach cancer, such as one or more first degree relatives with this condition, or the presence of gastric mucosal dysplasia found at gastroscopy, it seems reasonable to offer *H. pylori* eradication therapy. It is important however, to discuss with the patient, the possible side effects of the treatment, the lack of evidence to support this practice and the possibility of treatment failure (Dajani and Klamut, 2000).

Triple drug therapy

Triple therapies with Lansoprazole, Amoxicillin and

Clarithromycin for eradication of *H. pylori* were studied in multicentric, randomized double blind fashion to evaluate the eradication rate and safety in Japanese patients with *H. pylori* positive active peptic ulcers. Both regimens gave satisfactory eradication rates of *H. pylori* in patients with gastric ulcer or duodenal ulcer. The triple therapy with LPZ 30 mg/AMPC 750 mg/CAM 200 mg bid may be preferred in Japan because of the excellent rates and lower rate of side effects (Ahuja et al., 1998).

Quadruple treatment

Addition of acid suppressant increases the efficacy of bismuth triple regimen. Quadruple treatment is more effective with proton pump inhibitor than with histamine 2 receptor antagonists and when tetracycline and metronidazole are incorporated. In meta-analysis, the quadruple regimen with increasing number of tablet as dosage form design each day are presented and analyzed. Nevertheless studies have found good compliance with a drop out rate compared with that of the easier triple therapies. A course for seven days seems to cure both metronidazole sensitive and resistant strains. Sensitive strains as mentioned are eradicated in four days. The high cure rate at day 4 shows its potency and wide therapeutic window (Hoffman, 1999).

Recommendations for therapy

Currently, the indication for treatment of *H. pylori* infection should confirm to establish guidelines as per the National Institute of Health (NIH) and the Indian consensus statements (Tandon, 2000). When the treatment is indicated, the regimen selected should have a known eradication rate of over 90%, which is according to the recommended guidelines for the treatment of *H. pylori* infection. Local (geographical) prevalence of antimicrobial resistance should be known so that drugs can be combined appropriately. Additional factors to be taken into account include cost, simplicity of the schedule to avoid noncompliance and side effects. As mentioned earlier, a proton pump inhibitor based triple therapy regimen with two antibiotics for duration of 7 to 14 days has come to be accepted as the first line of optimal therapy. European reports favour a one-week therapy (two antibiotics, two adjunctive agents) compared to 10 to 14 days therapy recommended by the Americans (De Boer and Titrato, 1995). In countries like India and Pakistan, where resistance to nitroimidazoles is high, it is better to avoid this class of drugs when choosing a combination therapy. It is preferred to use a PPI with amoxicillin and clarithromycin as the first line of treatment for duration of 10 days. An alternative line of therapy can be Ranitidine bismuth citrate in combination with amoxicillin and clarithromycin. Amoxicillin can be substituted with metronidazole when the local resistance

to nitroimidazoles is low. Quadruple regimens are good as second line therapy for failed primary treatment. A triple regimen with a PPI and different combination of antibiotics not used earlier can also be tried. The duration of the treatment in this instance should be increased to increase the likelihood of cure. Although a seven day treatment is standard for PPI and Ranitidine Bismuth Citrate based regimens, the success rate can be improved by prescribing a 10 to 14 day regimen in patients who have had previous drug failure. Confirmation of eradication of *H. pylori* is not recommended in every case treated for *H. pylori* when an optimal regimen is used and patient compliance is good. However, confirmation of eradication might be required in patients with a history of ulcer complications or following treatment for MALT lymphoma. Most of the tests for confirming eradication are invasive and require endoscopy. Urea breath tests are recommended in guidelines as a preferred non-invasive choice for detecting *H. pylori* before and after treatment (Chey, 2007).

Conclusions

Triple therapy regimens comprising of a proton pump inhibitor or ranitidine bismuth citrate and two antibiotics (amoxicillin and clarithromycin) are the standard therapy to treat *H. pylori* infection. Bismuth based triple therapy consisting of bismuth, tetracycline and metronidazole is less expensive as compare to proton pump inhibitor or ranitidine bismuth citrate based triple therapies. However, bismuth triple therapy manifest by side effects and metronidazole resistance in Asian countries like India and Pakistan. In Europe, a 7 day course of PPI based triple therapy is usually recommended, whereas, in USA, the same dosage prescribed is of 10 to 14 days. It is recommended 10-day triple therapy in a combination, which does not include nitroimidazoles. Clarithromycin resistance is also rising in countries where this antibiotic is widely prescribed for other infections. If a patient remains infected after a course of therapy for *H. pylori*, the second treatment should avoid the antibiotics that cause resistance. If the first line PPI based therapy fails, either an RBC based triple therapy or quadruple therapy consisting of a PPI and bismuth triple therapy combination is recommended. The antibiotic resistance in bacteria and understanding of its mechanism or eradication has to explored for the ultimate eradication of *H. pylori* infection.

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