It took more than 15 years for Warren and Marshall to get their discovery of *Helicobacter (H.) pylori* recognized internationally, they went on to secure a Nobel Prize for this feat. It can only be wondered if they knew that *H. pylori* would be the bane of the 21st century, being the most common chronic infection worldwide. It has changed peptic ulcer disease (PUD) into an infectious disorder; further *H. pylori* has become the most over-diagnosed and treated infection especially in under-developed and developing countries like Pakistan. Scores of patients repeatedly get treated for *H. pylori* eradication on the basis of positive anti-body titers. Evidence-based studies have improved the understanding of this complex micro organism with respect to its pathogenicity and pathogenesis, diagnosis and devising treatment strategies.

*H. pylori* is the most common worldwide human infection, being more prevalent in developing than developed countries, the prevalence being directly proportional to the economic conditions. The prevalence has been declining rapidly in developed countries like U.S.A where still 30-40% of the population is said to be infected, the number being higher in non-whites and immigrants. This infection is mainly acquired in infancy and childhood, transmission being from person to person. In Pakistan the data about the prevalence of *H. pylori* is scanty but earlier studies showed seroprevalence of 58-60%.

*H. pylori* infection has been etiologically related to important gastric conditions that is peptic ulcer disease, chronic gastritis, MALT lymphoma and gastric cancer. Association with other important conditions is coming up on the basis of studies these include functional dyspepsia, unexplained iron deficiency anemia and chronic ITP. As majority of patients with *H. pylori* infection do not have any related significant disease, routine testing in population is not advisable. Definite indications for testing are, proven peptic ulcer disease, gastric MALT lymphoma and gastric carcinoma (Ca). Maastricht guidelines also recommend testing and eradicating *H. pylori* infection in first degree relatives of patients with Ca stomach, patients with atrophic gastritis, unexplained iron deficiency anemia, and chronic idiopathic thrombocytopenic purpura. Patients with functional dyspepsia (uninvestigated) may be tested and treated for *H. pylori* infection, reason being cost effectiveness as well avoiding endoscopic examination in many patients. However, endoscopy is mandatory in patients having significant weight loss, intractable vomiting and in elderly patients.

The success of eradication of *H. pylori* infection is not only dependent upon the treatment regimen but also upon the knowledge of primary care physicians about the organism itself, indications for its eradication, the diagnostic tests used and the practice of follow-up after eradication.

There are different diagnostic tests available for the diagnosis of *H. pylori* infection which can be subgrouped into non invasive (serology, urea breath test and stool antigen testing) and invasive (endoscopy, histopathology, culturing from tissue and PCR) method.

Serology is widely available and relatively inexpensive test with 85% sensitivity and 79% specificity. Major limitations of serology are that the antibody titers may remain high for months or even years after treatment. A recent large cohort study carried out on physicians in Pakistan has shown that 43% physicians considered serology as the investigation of choice, whereas 47% preferred serological follow-up after eradication. Serology based tests have no current role in the management of *H. pylori* infection. The detection of specific *H. pylori* antibodies in urine and saliva also has no current role in patients management. According to Maastricht III consensus report the serological diagnosis has no or limited role in the management of the *H. pylori* infection. Serological diagnoses can be considered in patients with bleeding ulcers, gastric atrophy, MALT lymphoma, recent or current use of PPI (Proton Pump Inhibitors) and antibiotics where other test may be falsely negative. As rapid urease test, culture, and histology as well as UBT have shown limited sensitivity in patients with acute bleeding peptic ulcer.

Stool antigen testing for *H. pylori* has shown 91-95% sensitivity and 94-99% specificity. Stool antigen testing is a good alternative to UBT and can be used to confirm eradication even just after seven days, easy to perform and independent of age. Stool antigen test has some limitations that is results may be altered in patients on...
PPIs/antibiotics and having bleeding ulcers in later case of polyclonal stool antigen test has a low specificity due to cross reactivity with blood products, so in some cases monoclonal antibody based test is more reliable.

Urea breath test (UBT) has the highest sensitivity (95-100%) and specificity (91-95%) thus being a reliable tool among the non invasive tests for detection of *H. pylori*. UBT is the best available diagnostic test for children but has some limitations like higher false positive rates in children younger than 6 years of age compared to school age children and adolescents, reduced sensitivity due to use of PPIs, antibiotics and bismuth containing compounds.10

Among invasive test for *H. pylori* endoscopic biopsy for histology has a sensitivity of 95% and specificity of 100% but sensitivity may be reduced by the use of PPIs, antibiotics, bismuth containing compounds and test is also time consuming.

Determination of Urease activity (sensitivity of 97% and specificity of 95%) is another way to detect *H. pylori* but its sensitivity can be reduced by PPIs, antibiotics and bismuth containing compounds.7 Among the group of invasive tests PCR (Polymerase Chain Reaction) testing for *H. pylori* is highly specific and may be more sensitive than biopsy-based diagnostic techniques. Apart from detection of *H. pylori* it also provides a mean of identifying mutations associated with antimicrobial resistance. Although PCR is presently restricted to the field of research, but in future may provide a valuable method for antibiotic sensitivity testing, organism typing, and organism virulence testing. 10 Culture of *H. pylori* is highly specific invasive test (sensitivity 80% and specificity 79%) but, test is technically demanding and not freely available.10

As far as eradication therapy of *H. pylori* is concerned, ACG (American College of Gastroenterology) has issued established and possible indications.7 The established indications are active peptic ulcer disease (gastric or duodenal ulcer), confirmed history of peptic ulcer disease (not previously treated for *H. pylori*), and patients with gastric MALT lymphoma, in one large study 62% patients showed complete remission after 12 months of eradication.10 Other indication include following endoscopic resection of early gastric cancer and uninvestigated dyspepsia (depending upon *H. pylori* prevalence).

The possible (or controversial) indications for *H. pylori* eradication are non-ulcer dyspepsia, gastro-esophageal reflux disease, patients using uncontrolled NSAIDS, unexplained iron deficiency anemia and populations at higher risk for gastric cancer.

Maastricht consensus report III has also formulated guidelines or recommendations for eradication of *H. pylori* infection, which are similar to the above guidelines but have included certain further indications for eradication in NSAIDS-induced ulcer, as in the naïve NSAID-user, *H. pylori* eradication may prevent peptic ulcer and bleeding.10 Patients with long term use of PPI along with corpus dominant gastritis also require eradication since studies show that eradication of *H. pylori* in patients with profound acid suppression may prevent atrophic gastritis. In severe iron deficiency anemia and chronic ITP, recent studies showed that *H. pylori* eradication resulted in an increase in numbers of platelets and reversal of iron deficiency anemia.7

Selection of therapeutic regimen for *H. pylori* eradication is important for success. Predominant causes of failure to eradication are inadequate doses, short duration of treatment and resistance to drugs. Maastricht consensus report and ACG 2007 guidelines10,7 recommended first line regimen for *H. pylori* eradication should be a PPI in a standard dose twice a day (b.i.d) except for esomeprazole 40 mg is to be given once a day (q.i.d), clarithromycin (500 mg b.i.d), amoxicillin (1000 mg b.i.d) or PPI, clarithromycin (500 mg b.i.d) and metronidazole (400 or 500 mg b.i.d) for 10-14 day treatment (eradication rates 70-85%). Despite international recommendations for a 7-day therapy for eradication, the large evidence-based data still confirms that 10-14 days therapy is more effective than 7 days by 12% (95% confidence interval 7-17%).10 A 7-day treatment may be acceptable where local studies show its equal or better comparative efficacy.

PPI-clarithromycin-amoxicillin treatment is the recommended first line of treatment in patients who are non penicillin allergic, have not previously received a macroloid and populations with less than 15-20% clarithromycin resistance.10 In populations with less than 40% metronidazole resistance and penicillin allergic patients, PPI-clarithromycin-metronidazole is the preferable regimen.

Quadruple regimens are the alternate choice comprising of Bismuth subsalicylate 525 mg q.i.d, metronidazole 250 mg q.i.d, tetracycline 500 mg q.i.d, and ranitidine 150 mg b.i.d or standard dose PPI q.d to b.i.d for 10-14 days especially in penicillin-allergic patients.10 The quadruple therapy has eradication rates of 75-90% but is criticized because of its complexity (q.i.d dosing and high pill count).10

Recently a sequential therapy for *H. pylori* eradication has been proposed as an alternative to clarithromycin-based triple or bismuth quadruple therapy, it comprises of a PPI and amoxicillin for 5 days followed by a PPI, clarithromycin and tinidazole for an additional 5 days with an eradication rate of > 90% although requires further validation.10

The confirmation of successful eradication is another area of concern, as mentioned earlier many physicians follow the antibody titers which causes unnecessary repetition of eradication therapy. Maastricht guidelines
recommend that \textit{H. pylori} eradication should be confirmed at least four weeks after the treatment by urea breath test if available or otherwise fecal antigen testing with monoclonal antibodies.\textsuperscript{10}

In patients where eradication fails salvage or rescue therapy should be considered for persistent \textit{H. pylori} infection.\textsuperscript{7,10} The two recommended regimens include Bismuth quadruple therapy (PPI q.i.d. tetracycline, pepto Bismol, metronidazole q.i.d. for 7 days with claimed eradication rates of 68%\textsuperscript{7}; or Levofloxacin triple therapy (PPI, amoxicillin 1 g b.i.d and levofloxacin 500 mg q.i.d for 10 days with eradication rates of 87%)\textsuperscript{10} but this still requires further validation.

As is obvious from the above discourse, \textit{H. pylori} infection from diagnosis, treatment and final evidence of eradication is complex at best. Where patients gravitate towards primary care physicians, there are two scenarios on opposite sides. One aspect is under diagnosis, whereas at the other end is poor management by too much emphasis on serology as an evidence of diagnosis and eradication. It would be simpler to use urea breath test and fecal antigen testing for diagnosis and evidence of eradication. The use of serology should be limited for diagnosis and that also only once and with definite indication.

In conclusion, established indications should be actively investigated for evidence of \textit{H. pylori}. Also besides established indications there are upcoming situations where \textit{H. pylori} should be investigated and treated. Triple therapy comprising of a PPI, clarithromycin and amoxicillin is still the preferred first line treatment but eradication rates are decreasing worldwide. Sequential therapy and alternate Levofloxacin-based regimens are showing good results but need further controlled studies to support the efficacy.

\textbf{REFERENCES}