Helicobacter pylori - The Legendary Bug

Dr. Carmen Ng

MBBS, MRCP, FHKCP, FHKAM (Medicine)
Associate Consultant, Department of Medicine and Geriatrics, Princess Margaret Hospital, Kowloon, Hong Kong

Helicobacter pylori is a helical shaped, microaerophilic, flagellated Gram-negative bacterium. Its discovery dated back to 1875 but it could not be grown in culture at that time. In 1979, the bacterium was rediscovered by Dr. Robin Warren. Dr. Barry Marshall joined the research in 1981. They published the association of the bacteria and gastritis in 1983. In recognition of their discovery, Drs. Warren and Marshall became Nobel Laureates in 2005.

Epidemiology

Nearly half of the world population is infected with H. pylori. Its prevalence correlates inversely with the socio-economic status of a country. Using a commercial enzyme-linked immunosorbent assay kit for anti-HP IgG antibody on 397 volunteers who attended medical health exhibitions in October 1993 and May 1994, prevalence of H. pylori infection was found to be 58.4% in Hong Kong. More than 90% of duodenal ulcer patients were infected. Positive H. pylori positive patients develop duodenal ulcer at a rate of ~ 1% per annum. A lower prevalence of H. pylori is observed in patients with gastric ulcer, a higher proportion of which is related to the use of aspirin and non-steroidal anti-inflammatory drugs.

The bacteria have been isolated from faeces, saliva and dental plagues of infected patients. The routes of transmission are suggested to be gastro-oral and faecal-oral. An epidemiological study performed in Melbourne Chinese immigrants showed the use of chopsticks as a risk factor for H. pylori infection, irrespective of their socio-economic status. Leung et al. tested the hypothesis of transmission via the use of chopsticks by attempting to culture the bacteria from saliva and chopsticks of 45 infected volunteers. All cultures were negative. H. pylori was detected by PCR in the saliva from 15 (33%) infected subjects and on the chopsticks from one (2%). Twelve sets of pooled chopsticks, ten in each set, were collected from the cafeteria. Washings were obtained for PCR. H. pylori was tested positive in only two sets. This demonstrated a low risk of contracting the infection through the use of chopsticks.

Diagnosis

Various diagnostic tests are available in the market. Basically they can be divided into invasive and non-invasive tests. Invasive tests include biopsy-based rapid urease test, histology, culture and molecular tests. Non-invasive tests can further be classified into passive and active tests. Passive tests include serological testing of IgG in serum, IgA in saliva, and IgG in urine. There is a trend towards development of the office-based serology tests for rapid diagnosis. A Canadian study performed for dyspeptic patients in the primary care setting, however, found a high false positive rate of 33%. It is still early to recommend the use of near-patient tests for making a diagnosis of H. pylori infection. Active tests serve to detect the presence of H. pylori and hence they provide evidence of a current infection. Currently available active tests include the urea breath test and stool antigen test.

Before a test can be employed in the community, local validation of its accuracy is required. Tests can be done by a technician but their interpretations require medical knowledge. The accuracy of biopsy-based rapid urease test is decreased in the setting of acute ulcer bleeding due to the buffering effect of serum albumin. Albumin, by releasing hydrogen ions, buffers the alkaline effect of ammonia and suppresses the colour change of the pH indicator. It was found that H. pylori was detected in 93% of nonbleeding duodenal ulcers as compared with 71% of bleeding duodenal ulcers by the biopsy urease test. There were cases where the bacteria, failed to be detected by biopsy urease test, were identified by histology.

Achlorhydria causes false-negative urease test results (biopsy and breath tests). Without the neutralising effect of acid, H. pylori is killed by the action of its own urease. Proton pump inhibitor (PPI), antibiotics and bismuth-containing compounds can reduce the density and / or urease activity of H. pylori. When given a standard dose of PPI for treating gastro-oesophageal reflux disease, 33% of the H. pylori-infected patients were tested negative by the urea breath test. Their tests returned positive 14 days after stopping the drug. Serial changes of urea breath test results in hospitalised patients taking antibiotics for chest or urinary tract infection were studied. One third of H. pylori-infected individuals had transient false-negative results. It occurred within 24 hours of antibiotics treatment and reverted back to normal at six-week post treatment.

It has been recommended to withhold bismuth and antibiotics for at least 28 days and PPI for 14 days prior to H. pylori testing by the urea breath test. It is controversial whether H2-receptor antagonists affect test sensitivity but most laboratories would suggest to
withhold it for 48 hours before testing.\textsuperscript{17} Despite the high sensitivity of histology, the site, numbers and size of the biopsies can have great impact on diagnostic accuracy. A single biopsy taken in the lesser curvature, close to the incisura, can detect the presence of \textit{H. pylori} in 90\% of the cases.\textsuperscript{12} Accuracy can be improved by taking additional biopsies from the greater curvature of the antrum and the greater curvature of the corpus. The American College of Gastroenterology has recommended a minimum of three biopsies to be taken for diagnosis.\textsuperscript{17}

\section*{Treatment}

The backbone of eradication therapy remains unchanged in all these years. Standard first line treatment comprises of a PPI and two antibiotics. A one-week course of this triple therapy was endorsed by The Asia-Pacific Consensus Conference\textsuperscript{20} in 1997 and The Maastricht III Consensus Report\textsuperscript{21} in 2007. In the United States, the same therapy is recommended to be given for 10 to 14 days.\textsuperscript{17} The efficacy of triple therapy has been decreasing to about 80\%.\textsuperscript{22} The drop in effectiveness is related to a rising trend of antibiotic resistance. Choice of antibiotics should be determined by the level of resistance in the locality. The European Helicobacter Study Group recommended that clarithromycin should not be used if the resistance rate reaches 15-20\%.\textsuperscript{23} In vitro metronidazole resistance is less of a concern since it does not reflect in vivo resistance. The prevalences of resistance to clarithromycin, amoxicillin and metronidazole in Hong Kong were 7.8, 0 and 39.2\% in a recent report.\textsuperscript{23} Bismuth-containing quadruple therapy has been suggested as an option for first line treatment in view of the increased resistance to both clarithromycin and metronidazole.\textsuperscript{24} Besides antimicrobial resistance, patients' compliance plays a role in determining the success of treatment. Eradication rate dropped from 96\% to 69\% in patients who took less than 60\% of their prescribed medication.\textsuperscript{24} Although it is common to experience taste disturbance with clarithromycin and metronidazole and diarrhoea with amoxicillin, they are usually mild. Patients should be assured on the short-term nature of the side effects and encouraged to complete the course.

\section*{Sequential Therapy}

A novel 10-day sequential therapy was shown to be effective in a number of studies carried out in Italy.\textsuperscript{25-28} It consists of 5-day dual therapy with a PPI plus amoxicillin, followed by 5-day triple therapy with a PPI, clarithromycin and tinidazole. Amoxicillin has dual actions. First it helps to lower the bacterial load so as to improve the efficacy of the immediately subsequent short course of triple therapy.\textsuperscript{29} Secondly, it is speculated that, after weakening the cell wall of the bacterium, amoxicillin prevents the development of efflux channels through which clarithromycin is transferred out of the bacterium.\textsuperscript{28} In a pooled-data analysis\textsuperscript{29} of two pilot studies and 13 randomised trials on over 1800 patients, sequential therapy achieved \textit{H. pylori} eradication rate of 93.5\% at intention to treat analysis. It was found to be promising in treating antibiotics resistant organisms. Infection was cured in 16/48 patients (33.3\%) infected with clarithromycin (with or without metronidazole) resistant strains, and 68/72 patients (95.8\%) infected with metronidazole resistant strains. Compliance and side-effect profile were comparable to standard triple therapy. No difference in eradication rate was observed among different PPIs, and between patients suffering from peptic ulcer or non-ulcer dyspepsia. This new regimen, however, is not suitable for patients with penicillin allergy and its effectiveness has to be verified by centres in other parts of the world.\textsuperscript{22}

\section*{Rescue Therapy}

The principle for choosing a rescue therapy is to avoid using antibiotics which have been used in first line treatment.\textsuperscript{17} Quadruple therapy, if not given as the first line treatment, is a preferred option.\textsuperscript{21} Recently levofloxacin-amoxicillin-based triple therapy was found to be superior to quadruple therapy in two meta-analyses.\textsuperscript{30, 31} It was found to be better tolerated with a lower incidence of side effects prompting discontinuation of therapy.\textsuperscript{31} Ten-day regimens, giving an eradication rate of over 80\%, were more effective than 7-day combinations.\textsuperscript{30, 31} While no difference was observed with 500mg daily versus 250mg bd dosing of levofloxacin.\textsuperscript{31} Emergence of levofloxacin resistant strains, however, may limit its application. It is still unknown whether the resistance is absolute, as in the case of clarithromycin, or more relative as with metronidazole.\textsuperscript{17} The ten-day therapy was found to be effective in a pilot study on 35 patients who had failed the sequential regimen. The eradication rate was 85.7\% at intention-to-treat analysis.\textsuperscript{32} Rifabutin-based triple therapies were tested by several groups and found to be useful as salvage therapy.\textsuperscript{33-36} The presence of clarithromycin or metronidazole resistance did not affect efficacy of treatment.\textsuperscript{36} It is, however, limited by the potential adverse reactions characterised by fever and myelotoxicity. Large-scale use of this drug is not advisable for the fear of selecting resistance among Mycobacteria.\textsuperscript{21}

\section*{Gastric cancer}

The incidence of gastric cancer in Hong Kong is 15.6 per 100,000.\textsuperscript{37} Over 1000 new cases were diagnosed in 2005. The average mortality rate was 9.3 per 100,000. \textit{H. pylori} was classified as a grade 1 carcinogen by the International Agency for Research on Cancer in 1994.\textsuperscript{38} The infection is associated with approximately two-fold increased risk of developing gastric cancer,\textsuperscript{39} equally strong for both the intestinal and the diffuse type.\textsuperscript{40} This association is only observed for cancers developed in the non-cardiac region.\textsuperscript{41} CagA positivity further increased the risk of cancer by 2.01 fold. Searching for CagA status over \textit{H. pylori} infection may confer additional benefits in identifying populations at greater risk for gastric cancer.\textsuperscript{42} But this association may not be true in the Asian population.\textsuperscript{42} In a prospective follow-up of more than 1500 Japanese patients suffering either from upper GI pathology (peptic ulcers or gastric hyperplasia) or nonulcer dyspepsia, gastric cancers developed in 2.9\% of the infected patients after a mean of 7.8 years, but not in the uninfected individuals.\textsuperscript{43} Histology findings of corpus-predominant gastritis, severe gastric atrophy, and intestinal metaplasia put patients at an increased risk. These histological findings...
were proposed as precancerous cascade in the development of gastric cancer. Apart from the infection, host genetic and environmental factors also contribute to the risk. It remains unknown whether H. pylori eradication would reduce the risk of gastric cancer. It is unlikely that by simply removing the organism will translate into a perceptible reduction in gastric cancer risk within a short time frame. There are a number of human intervention studies looking into the effect of H. pylori eradication in the progression of precancerous lesions. It leads to the concept of ‘point of no return’.

The Chinese University of Hong Kong and the Beijing Medical University conducted a collaborative study in the county of Yantai, Shandong Province, China, where there is a high incidence (50 per 100,000) of gastric cancer. Endoscopic surveys were conducted. 587 H. pylori infected volunteers were randomised to triple therapy or placebo. Both acute and chronic gastritis decreased in both the gastric antrum and corpus and activity of intestinal metaplasia also decreased in the antrum one year after H. pylori eradication. There was, however, no regression of intestinal metaplasia or gastric atrophy. Within 5 years after H. pylori eradication, remarkable reduction in severity and activity of chronic gastritis and marked resolution of intestinal metaplasia in the antrum were observed. Continuous H. pylori infection leads to progressive aggravation of atrophy and intestinal metaplasia. In their separate report, duodenal ulcer was found to be an independent protective factor, while persistent H. pylori infection, alcohol use and drinking water from a well were independent risk factors associated with intestinal metaplasia progression. They concluded that eradication of H. pylori is protective against progression of premalignant gastric lesions. A randomised, controlled chemoprevention trial conducted in Columbia showed that by curing H. pylori infection, a modest regression of intestinal metaplasia compared with placebo (15% vs 6%) was observed after 72 months. In their multivariate analysis at 12 years of follow-up on 795 patients, the preneoplastic lesions were found to regress at a rate equal to the square of time patients having free from the infection.

A randomised controlled trial was conducted in Changle Medical University conducted a collaborative study in the county of Yantai, Shandong Province, China, where there is a high incidence (50 per 100,000) of gastric cancer. Endoscopic surveys were conducted. 587 H. pylori infected volunteers were randomised to triple therapy or placebo. Both acute and chronic gastritis decreased in both the gastric antrum and corpus and activity of intestinal metaplasia also decreased in the antrum one year after H. pylori eradication. There was, however, no regression of intestinal metaplasia or gastric atrophy. Within 5 years after H. pylori eradication, remarkable reduction in severity and activity of chronic gastritis and marked resolution of intestinal metaplasia in the antrum were observed. Continuous H. pylori infection leads to progressive aggravation of atrophy and intestinal metaplasia. In their separate report, duodenal ulcer was found to be an independent protective factor, while persistent H. pylori infection, alcohol use and drinking water from a well were independent risk factors associated with intestinal metaplasia progression. They concluded that eradication of H. pylori is protective against progression of premalignant gastric lesions. A randomised, controlled chemoprevention trial conducted in Columbia showed that by curing H. pylori infection, a modest regression of intestinal metaplasia compared with placebo (15% vs 6%) was observed after 72 months. In their multivariate analysis at 12 years of follow-up on 795 patients, the preneoplastic lesions were found to regress at a rate equal to the square of time patients having free from the infection.

Reinfection

After successful H. pylori eradication, how often would we get re-infected? Re-infection should be distinguished from recrudescence which usually occurs early after treatment. It means reappearance of the original strain of H. pylori following its temporary suppression. One would expect high reinfection rates in countries with high prevalences of H. pylori infection. Reinfection rate was determined in 184 Chinese patients with duodenal ulcer disease who had been shown to have their H. pylori eradicated. It was conducted in Guangzhou, with a high age-standardised prevalence of ~56%. Over a period of 24 months, four patients were tested positive for H. pylori (three within six months and one at 24 months). DNA fingerprinting of isolates in one patient diagnosed H. pylori positivity at 6 month was found to have a strain identical to the pretreatment one. The average annual reinfection rate was found to be 1.08%. Similarly low rates of re-infection were found in other Asian countries. If identical strains were considered as recrudescence, the reinfection rate was found to be < 0.8% per patient year in a Japanese study over a period of two years.

References

Secretariat at 2527 8898 or info@fmshk.org for further information and assistance.

Please fill in the order form if you wish to purchase extra hard copies and/or CD ROM or contact the

We apologise for the delay in the production of the Directory, as it took an unexpectedly longer time to do the

The Federation Secretariat will notify those who have submitted their data regarding arrangement of delivery.

On behalf of the Editorial Board, it is our great pleasure to announce the launch of the Medical & Dental

As the delay was unexpected, we would like to apologise to the Federation Secretariat for the inconvenience caused. We appreciate your understanding and patience.

Please fill in the order form if you wish to purchase extra hard copies and/or CD ROM or contact the Secretariat at 2527 8898 or info@fmshk.org for further information and assistance.

Please note that the Directory is not for public sale. Its distribution is confined to healthcare professionals.