CURRENT VIEWS ON TREATMENT OF PEPTIC ULCER DISEASE

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Schwartz’s dictum of “No acid – on ulcer”¹, having stood for so long probably has now to be modified to “No Helicobacter pylori – on ulcer”² to incorporate modern concepts of peptic ulcer disease³. It has now been established beyond reasonable doubt that Helicobacter pylori is the main aetiological agent contributing to the pathogenesis of peptic ulcer²⁴. This concept has revolutionized the clinical approach to peptic ulcer disease⁵. Peptic ulcer can now be more effectively cured by a single course of antibiotic therapy rather than continuous suppression of acid secretion. Such a view of ulcer pathogenesis and treatment has been endorsed by the recent recommendations of the Consensus Development Conference of the National Institutes of Health (N.I.H.) of the United States, which recommends that all Helicobacter pylori infected peptic ulcer patients should receive antimicrobial therapy⁶.

This review will focus mainly on diagnosis and treatment of Helicobacter pylori in peptic ulcer disease.

The Role of H. pylori in Peptic Ulcer disease

Much evidence has accumulated (for review, see reference⁷ to support the concept, first proposed by Marshall⁸ that Helicobacter pylori contributes to peptic ulceration.

Three lines of evidence suggest that gastritis induced by Helicobacter pylori is a major factor in causing peptic ulcers, especially duodenal ulcers. First with the exception of those patients taking non-steroidals anti-inflammatory drugs and patients with Zollinger Ellison Syndrome or Crohn’s disease, more than 95% of the patients with duodenal ulcers and 80% of the patients with gastric ulcers have been shown to be infected with Helicobacter pylori⁹¹⁰. Secondly, many studies have shown a strong association between development of duodenal ulcer and presence of Helicobacter pylori; in most studies, more than 90% of the duodenal ulcer patients were shown to harbour Helicobacter pylori¹⁰¹¹. Thirdly, the relapse rate of the duodenal and gastric ulcer is markedly reduced by the eradication of Helicobacter pylori. Many studies have confirmed that successful eradication of the microorganisms can reduce the relapse rate, to virtually zero in some cases¹²²⁵.

Despite the fact that Helicobacter pylori is necessary for the development of peptic ulcers in most patients, it most
patients, it is from sufficient. Indeed only small proportion (10-15%) of infected patients go on to develop peptic ulcer. Why infection with Helicobacter pylori leads to development of peptic ulcer in only a minority of infected persons is not clear. To date, no consistent pattern of factors has been identified in either the host or the organism that will predict which infected persons will subsequently develop peptic ulcer disease.

**Diagnosis of Helicobacter pylori infection**

Helicobacter pylori can be detected either by an endoscopically based and therefore invasive tests or by various non-invasive methods. The non-invasive methods available for diagnosis of Helicobacter pylori infection involve either serological tests or breath tests, based on the hydrolyses of infested labeled urea by the bacteria and exhalation of the products in the breath.

Chronic infection with Helicobacter pylori is associated with an antibody response that can be detected by various serological assays like complement fixation, haemagglutination, bacterial agglutination, immunofluorescence and enzyme linked immunosorbent assay (ELISA). ELISA is currently the technique of choice and the latest “in office” whole blood ELISA test (Helisal-Cortecs Ltd) demonstrated a sensitivity and specificity of 91% in a study carried out by Mooyedi et al in Leeds UK. These tests are almost as sensitive and specific as methods involving biopsy which is the reliable method of choice for detection. Testing by serological methods is the least expensive of the various tests available for the initial diagnosis but is not useful verifying early eradication of the organism because antibody titres decrease slowly over a period of 6 to 12 months; and antibodies may remain detectable indefinitely in a substantial proportion of patients.

The urea breath test is a sensitive, specific, and non invasive but expensive method of detecting the presence of Helicobacter pylori infection.

The breath tests relies on the enzymatic hydrolysis of ingested urea to ammonia (NH3) & CO2 (labeled with either Carbon-14, a radioactive isotope but is cheaper or on Carbon-13 a stable but non radioactive isotope) by urease, an enzyme produced in high concentrations by Helicobacter pylori. The labeled carbon dioxide formed is rapidly absorbed into the blood stream from stomach and can then be detected in expired air. This requires a spectrometer. This test is sensitive and specific in both the initial diagnosis of Helicobacter pylori infection and also in the follow-up post eradication treatment. It is unreliable in patients who have had stomach operations and cannot be used in children or pregnant women since C14 is a radioactive isotope.

Diagnosis in patients on whom endoscopy is being performed can be made by taking mucosal biopsies. The presence of Helicobacter pylori can be confirmed by direct histological examination of the specimen, by culture of the biopsy material under special micro aerobic conditions or by performing the (Campylobacter like organism, CLO) test in the endoscopy suite on the biopsy specimen taken. For CLO test, the gastric biopsy specimen is placed in urea broth or agar. The test detects the presence of preformed urease produced by Helicobacter pylori in the biopsy specimen. The urease hydrolyses urea in the broth with the production of ammonium ions which raises the pH. The pH change is detected by pH indicator phenol which changes colour from yellow/brown at pH 6.8 to pink at pH 8.4. A buffer is present in broth to increase its stability and reduce false positives. A colour change
from yellow/brown to pink is considered positive for the presence of Helicobacter pylori\textsuperscript{38}. The CLO test currently the most commonly used test in clinical practice for Helicobacter pylori detection.

**Treatment of Helicobacter pylori**

Helicobacter pylori infection is inherently difficult to eradicate and 100% eradication has not yet been achieved\textsuperscript{39-42} with any of the treatment regimes. Eradication has usually be arbitrarily defined as the absence of Helicobacter pylori as shown by biopsy or breath test, 4–6 weeks after the completion of a course of treatment. The failure to detect Helicobacter pylori may only reflect suppression of the infection and does not necessarily imply long term cure\textsuperscript{43}.

Various combinations of antibiotics and antisecretory therapies (see table 1), have been tried, with varying degrees of success. Helicobacter pylori is resistant to only a few antibiotics e.g. (vancomycin, trimethoprim and sulphonamide) but it readily becomes resistant to metronidazole and to a lesser extent clarithromycin if either agent is given alone\textsuperscript{44-46}. The combination of three antibiotics (triple therapy) has been shown to be the most efficacious. The drugs used were bismuth, metronidazole and tetracycline\textsuperscript{6,25,40,42} or bismuth, metronidazole and tetracycline for 14 days eradicated Helicobacter pylori in 86% of the patients studied\textsuperscript{41}. Treatment for a longer duration was more effective, than a shorter course regime\textsuperscript{42}. Substitution of tetracycline with amoxicillin with amoxicillin led to slightly lower (76%) cure rate\textsuperscript{42}. Addition of a proton pump inhibitor such as omeprazole 20 mg bd to seven day tetracycline based triple therapy led to 98% eradication rate\textsuperscript{47}.

Resistance to metronidazole reduced the eradication rate significant\textsuperscript{44,48} but even in these circumstances a 50–60% eradication rate can be achieved\textsuperscript{48}. To improve the results in the group of patients who are refractory, substitution of metronidazole with clarithromycin has been suggested\textsuperscript{41,49}.

A substantial number of patients have side effects on antibiotics based regimens including nausea, vomiting and diarrhea but only a few cease treatment prematurely\textsuperscript{42} especially if they have been warned of the possible side effect\textsuperscript{50}. In order to overcome the problems of side effects and complex

**POINTS OUT THE VARIOUS REGIMENS**

Eradication rates (% of patients free from infection) achieved by antibiotic regimens for treatment of Helicobacter pylori infection

<table>
<thead>
<tr>
<th>Triple therapy</th>
<th>Study</th>
<th>Duration</th>
<th>Eradication rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bismuth, Metronidazole &amp; Tetracycline</td>
<td>Penston [42]</td>
<td>14 days</td>
<td>86%</td>
</tr>
<tr>
<td>Bismuth, Metronidazole &amp; Amoxicillin</td>
<td>Penston [42]</td>
<td>14 days</td>
<td>76%</td>
</tr>
<tr>
<td>Dual therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole, Amoxicillin, Omeprazole</td>
<td>Hudson [51]</td>
<td>7 days</td>
<td>84%</td>
</tr>
<tr>
<td>Single agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin, Omeprazole</td>
<td>Byerdorff [53]</td>
<td>10 days</td>
<td>82%</td>
</tr>
<tr>
<td>Omeprazole, Clarithromycin</td>
<td>Logan [54]</td>
<td>14 days</td>
<td>83%</td>
</tr>
</tbody>
</table>

**TABLE - 1**
dosage regimens, double and single agent therapies are being tried.

The use of a single antibiotic in combination with a proton pump inhibitor looks an attractive combination for clinical practice. Initial reports suggest an 82% eradication rate with the use of 2g amoxicillin and 80 gm omeprazole but were not confirmed by subsequent studies. The combination of omeprazole 40 mgs plus clarithromycin 500 mg tid has been reported to achieve a 80% eradication rate and is being evaluated further.

The chance of reinfection after eradication is low for two reasons. Firstly, long term follow up studies show that adults have only 1% annual incidence of acquiring Helicobacter pylori. Secondly the success of eradication therapy is maintained. These observations make it likely that prospect of reacquiring the infection after successful treatment in adults at least in the Western world remains low. More studies would be required to substantiate the same observations in the developing countries.

In conclusion, the optimal therapeutic regime for Helicobacter pylori induced peptic ulcer disease is still to be found. On the current evidence, the first choice for treatment of Helicobacter pylori positive peptic ulcer should be a combination of an antisecretory drug triple therapy of bismuth, metronidazole and tetracycline with substitution of the metronidazole with clarithromycin in patients known to have taken metronidazole before or who are known to be resistant to it. The second choice regime should be a combination of an antisecretory drug plus two antimicrobial drugs such as metronidazole, amoxicillin or clarithromycin. The combination of a single antibiotic like amoxicillin plus a antisecretory drug like omeprazole awaits further evaluation.

Successful eradication of Helicobacter pylori with what ever antimicrobial therapy will hopefully make recurrent peptic ulcers a medical rarity in the 21st Century.

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