

# Tough Nut to Crack: H. Pylori

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**H**elicobacter pylori is a gram-negative, spiral, flagellated, motile, micro-aerophilic and slow-growing bacillus that colonizes the gastric epithelium. It was discovered by Warren and Marshall (1979-81). Helicobacter pylori is associated with type B gastritis (localized to antrum and pylorus) and is found in up to 95% of patients with duodenal ulcers and 80% of patients with gastric ulcers in some parts of the world.<sup>1</sup> It has been demonstrated by various studies that eradication of H. Pylori is associated with reduced recurrence of peptic ulcer disease.<sup>2,3</sup>

## Epidemiology

The infection is prevalent worldwide. The overall prevalence of H. pylori infection is strongly correlated with socioeconomic conditions. The prevalence among middle-aged adults is over 80% in many developing countries. Infection is acquired by oral ingestion of bacteria and transmission is prevalent in families and in early childhood.<sup>5</sup> In developing countries like ours, apart from person to person transmission, water can be an important source of acquiring infection. Most infections occurring in childhood are relieved spontaneously but infection acquired in adults is chronic and seldom improves without therapy.

## Pathogenesis

H. Pylori is unique and survives in the toughest environment of gastric mucosa.

Acidic media trigger cytoplasmic urease activity of Helicobacter pylori. UreI-mediated transport is urea specific, passive, nonsaturable, nonelectrogenic and temperature independent that functions as a H<sup>+</sup>-gated urea channel regulating cytoplasmic urease, essential for gastric survival and colonization.<sup>6</sup> Deletion of UreI prevents this activation of cytoplasmic urease that is essential for bacterial acid resistance. H. pylori manages to evade the immune mechanisms and leads to persistent colonization of gastric mucosa. The genome of H. pylori changes continuously during chronic colonization of an individual host by importing small pieces of foreign DNA from other H. pylori strains during persistent or transient mixed infection.<sup>7</sup> It binds tightly to epithelial cells by multiple bacterial-surface components like BabA, is a 78-kD outer-membrane protein that binds to the fucosylated Lewis B blood-group antigen.<sup>8</sup> Several other members of the Hop protein family also mediate adhesion to epithelial cells.

CagA is the gene responsible for secretion of highly immunogenic protein CagA protein which induces release of proinflammatory cytokines like interleukin-1 $\beta$ , interleukin-2, interleukin-6, interleukin-8, and tumour necrosis factor  $\alpha$ .<sup>9</sup>

H. pylori strains express the 95-kD vacuolating cytotoxin VacA, a secreted exotoxin<sup>10</sup> that inserts itself into the epithelial-cell membrane and forms a hexameric anion-selective, voltage-dependent channel through which bicarbonate and organic anions can be released possibly providing the bacterium with nutrients. VacA is also targeted to the

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mitochondrial membrane, where it causes release of cytochrome c and induces apoptosis.<sup>11</sup> The pathogenic role of the toxin is still debated.

### Carcinogenesis due to *H. pylori*

It has been classified as IARC type I carcinogen as per the sero-epidemiological case control studies. The basic components of the process as shown in this Fig. 1 are chronic active non-atrophic gastritis → multifocal atrophy → intestinal metaplasia (first complete, then incomplete) → dysplasia → invasive carcinoma.<sup>13</sup> *Helicobacter felis* infection in the C57BL/6 mouse model reproducibly results in the classic sequence of histologic changes seen in human infection. The mice responding with a Th1 cytokine pattern are susceptible to mucosal damage, whereas those responding with a Th2 cytokine pattern are resistant to atrophy and cancer formation.<sup>14,15</sup> Non-atrophic gastritis mostly localized in the antrum and prominent in the corpus (oxyntic) mucosa in patients who are on proton pump inhibitors. The presence of glands with gastric antrum phenotype in the oxyntic mucosa called as “antralization” of body of stomach or pseudo pyloric metaplasia have received lot of attention as this type of precancerous lesions are frequently seen in animal models.<sup>18</sup> The spasmodic polypeptide expressing metaplasia (SPEM) has been recognized as a cancer precursor and is associated with *H.*

*pylori* infection. Chronic inflammation is a critical component of *Helicobacter*-induced SPEM and in its absence SPEM cells don't progress from dysplasia to neoplasia. It has been shown that the mucosal changes are reversible with early bacterial eradication and may prevent progression to cancer.<sup>19</sup> Eradication of bacteria after long-standing infection decreases the proliferation rate, but does not return it to normal hence the risk of carcinogenesis exists.<sup>20</sup>

Recently, a population of cancer cells within tumours has been identified that serves to provide all of the cancer cells of the tumour, termed the ‘cancer stem cell’.<sup>21,22</sup> In presence of chronic inflammation Bone marrow derived cells (BDMC) may function as these cancer stem cells. Both cell types may express CD44 and the ABC transporter Bcrp1/ABCG269 on the cell surface, endowing both cell types with the stem cell-side population phenotype.<sup>23</sup> How does these BDMC get recruited in the gastric mucosa is still unknown. The loss or damage to peripheral stem cells allows BMDC to engraft within the stem cell niche and assume the stem cell function. It is likely that in this abnormal environment of an ongoing inflammation the BMDCs are able to initiate differentiation but fail to regulate growth programmes appropriately and progress instead through stages of metaplasia and dysplasia.<sup>24,25</sup>

Gastric epithelium undergoes dysplastic changes, nuclei are enlarged, hyperchromatic, irregular in shape, and devoid of polarity. The architecture is irregular; frequently forming closely packed tubular structures (adenomas) with irregular lumens. The atypical changes are present in deeper glands as well as in the surface epithelium. Dysplasia (low or high-grade) when breach the basal membrane, they are termed as

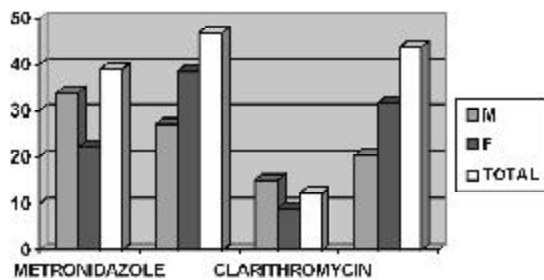


Fig. 1

invasive carcinomas.<sup>17</sup> There is general agreement that the dysplastic epithelium is neoplastic, therefore, dysplasia is also called intraepithelial neoplasia.<sup>17</sup> Dysplasia is uncommon in populations having low incidence of cancer. Progression of moderate to high grade dysplasia to invasive carcinoma is about 60-85% in various series.<sup>17,18</sup>

### **Diagnosis**

H. pylori infection can be diagnosed by various non-invasive or endoscopic biopsy of gastric mucosa. Noninvasive tests comprise serological tests for H. pylori, urea breath test, antigen testing (stool, saliva, and urine). Selection of tests for H. pylori infection should be based on the prevalence of H. pylori infection in the community and the pre-test probability of infection coupled with the cost and convenience of the test.

### **Serology**

There are different tests available for detection of antibody in the serum like including enzyme linked immunosorbent assay (ELISA), agglutination tests, and western blot but ELISA is the most widely used clinically. Antibody persists in blood for longer duration hence there is a high chance of false positive results. Overall sensitivity and specificity is 85% and 79% respectively with an overall accuracy of 78%.<sup>28</sup> Hence use of such serological tests with low accuracy is not justified in our set up on both clinical as well as economical grounds.

### **Urea Breath test**

In 1987 Graham described the first UBT specifically designed to detect H. pylori using urea labelled with the stable isotope <sup>13</sup>C or <sup>14</sup>C.<sup>29</sup> Urease enzyme present in H. pylori hydrolyses the urea producing isotopically labelled carbon dioxide.

A typical test in which 185 kBq of <sup>14</sup>C urea

is given, this gives radiation exposure to gonads and bone marrow of just  $3 \times 10^{-6}$  Sv, equivalent to roughly one day's background radiation. For UBT patient has to be fasting for 6 hours. The test is indicated for the initial diagnosis of the infection and for follow-up of eradication therapy. In the latter case, the urea breath test should not be performed before an interval of four weeks has elapsed, in order to avoid false negative results. Other causes of false negative test been high dose PPI, antibiotics and bismuth containing compounds. The urea breath test is reliable in children over the age of six years but needs further validation in younger children.<sup>30</sup> The test is with a sensitivity of 94.5% and specificity 95%.<sup>31,32</sup>

### **Stool antigen test**

Polyclonal anti-H pylori capture antibody absorbed to microwells is the most widely used test. This test has specificity of 92.8% and sensitivity of 93.1%. European Helicobacter pylori study group has recommended the use of the UBT or stool testing in the initial diagnosis of H. pylori infection.<sup>33</sup> The test performed after 4 weeks of eradication therapy has negative predictive value of 98% which is comparable to those obtained with <sup>13</sup>C UBT.<sup>31</sup>

### **Salivary and urine antibody assay**

Results are disappointing with tests specificity 73% and sensitivity of 81%<sup>34</sup> and can't be recommended in population where prevalence is more than 60% due to high false positive tests.

### **Endoscopy and Rapid Urease test**

When endoscopy is clinically indicated, the test of first choice is a rapid urease test on an antral-biopsy specimen.<sup>34</sup> Rapid urease test is 90% sensitive and specificity reaching to almost 100%.<sup>35</sup> Apart from H & E stain which is most commonly used, certain special stains

can be used for better identification of *H. pylori*. The most common special stains for *H. pylori* are WarthinStarry, Giemsa, Diff-Quik, and Genta. Periodic acid-Schiff combined with Alcan blue (pH 2.5) can be used to locate and characterize glycoproteins and also to enhance the detection of intestinal metaplasia or gastric carcinoma.<sup>37</sup>

*H. pylori* cultures are difficult to obtain and are generally not used in establishing a primary diagnosis because of the potential for false-negative results due to errors in specimen acquisition, storage, or transportation and its time-consuming nature (requires up to 2 weeks for growth to occur).<sup>38</sup> The performance of culture is useful for the determination of antibiotic resistance, especially in patients who continue to be positive for *H. pylori* after an initial treatment regimen.

### **Treatment of *H. pylori* Infection**

Indications for *H. pylori* eradication that were developed by an international consensus of experts<sup>39</sup> (Maastricht III Consensus Report) are listed in Table. Current US guidelines recommend testing and treatment for *H. pylori* in patients with uninvestigated dyspepsia in areas in which the prevalence of *H. pylori* is greater than 10%.<sup>40</sup>

### **Conventional regime**

Various triple drug therapy regime have been tried for varied duration from 7 days to 14 days to achieve eradication of *H. pylori*. The most recent trials have been as low as 57%–73%<sup>41</sup> (Bochenek *et al* 2003) and 67%–79%<sup>42</sup> (Vakil *et al* 2004) for 10-day triple therapy. A recent European study found no difference between 1 week and 2 weeks of PPI triple therapy.<sup>43</sup>

### **Bismuth-based triple/quadruple therapy**

In areas where metronidazole resistance

is low, Clarithromycin resistance is high Bismuth triple (bismuth + metronidazole + tetracycline for 14 days) and quadruple (bismuth + metronidazole + tetracycline + PPI for 7-10 days) therapies are effective treatment strategies. The major advantage of the bismuth triple therapy regimen is that it is inexpensive and can be used in regions of the world in which cost is the major consideration.

Eradication rates were similar with PPI triple therapy (78%) and quadruple therapy (82%), and both were significantly better than 14-day bismuth triple therapy (69%). The disadvantage has been pill load and cumbersome drug intake leading to poor compliance with therapy (15%) especially when taken for 14 days.

### **Sequential therapy**

The sequential regimen is a 10-day treatment consisting of a PPI and amoxicillin 1 g (both twice daily) administered for the first 5 days followed by triple therapy consisting of a PPI, clarithromycin 500 mg and tinidazole 500 mg BD for the remaining 5 days. The idea is based on the observations made when 2-drug therapies (PPI + amoxicillin) were in use. It was observed that the eradication rate achieved with a therapeutic strategy of initially administering 14-day dual therapy (PPI + amoxicillin) followed by 7-day triple therapy in individuals who failed the original therapy was significantly better than the reverse sequence (7-day triple therapy as an initial strategy with 14-day dual therapy for failures).<sup>46</sup> A recent head-to-head comparison of sequential therapy with conventional triple therapy found that 10-day sequential therapy had a significantly higher eradication rate (91% by modified intent-to-treat analysis) compared with 10-day triple therapy (78% by modified intent-to-treat analysis).<sup>47</sup> Use of low dose

clarithromycin in sequential therapy has also shown almost similar eradication rates.<sup>50</sup>

### **Resistance to anti-microbial therapy**

About one third of cases that failed to respond to therapy were found to be resistant to clarithromycin in a recent RCT in US.<sup>42</sup> In a multi-centre study from India, 259 isolates of *H. pylori* were tested for in vitro susceptibility to antibiotics; of these, 77.9% had resistance to metronidazole, 44.7% to clarithromycin and 32.8% to amoxicillin.<sup>44</sup> In another study of 67 clinical isolates of *H. pylori* from Kolkata, 85% were resistant to metronidazole and 7.5% to tetracycline, but most were sensitive to clarithromycin, furazolidone and amoxicillin.<sup>45</sup>

Resistance is acquired by various mechanisms.

Change in the 2 adjacent adenines on the 23S ribosomal RNA peptidyl transferase loop guanine or cytosine leading to a conformational change in the ribosome and a lack of binding of macrolides, avoiding the interruption of protein synthesis. Cross resistance is present in this class. Resistance of amoxicillin is acquired by mutations blocking the penicillin binding proteins rendering the drug ineffective.<sup>48</sup> Tetracyclines interfere with protein synthesis at the ribosome level by binding to the 30S subunit. Lack of binding to the h1 loop, the binding site for tetracyclines and efflux of drug confers resistance to this group of drugs.<sup>49</sup> Mutations responsible for resistance to all the class of drugs used in *H. pylori* eradication are listed in Table. Recurrence of this infection is rare in developed countries however no data of much significance could be cited for recurrence studies in India. In one Indian study of 45 patients followed up following eradication of *H. pylori*, recurrence of infection was detected in only one patient (2.4%) after one year.<sup>51</sup> However the incidence

of recurrence could be believed to be high in our set up and detailed studies are required to prove recurrence in Indian population.

Other factors affecting *H. pylori* eradication apart from antibiotic resistance could be responsible for difference in the eradication rate. Difference in the metabolism of drugs, use of different PPI the rates of eradication were lower with omeprazole but were similar with Rabeprazole and Lansoprazole.<sup>52</sup> Smoking has also been linked with high likelihood of failure eradication therapy.<sup>53</sup> Variable data on reduced rate of eradication in pts with non ulcer peptic disease.<sup>54</sup>

### **Failed eradication**

For the patient with failed eradication, 4 possible choices are available

- (1) Antimicrobial sensitivity testing and tailored therapy
- (2) Quadruple therapy
- (3) Sequential therapy
- (4) Salvage therapies.

Out of the 4 therapies suggested quadruple therapy and sequential therapy have already discussed and have shown very good outcomes in various trials.

Anti-microbial sensitivity testing can be done using Etest (a quantitative variant of disk diffusion), agar or broth dilution method, or break-point testing.<sup>60</sup> These methods have the advantage of evaluating all of the drugs at the same time, and, for most of them, an exact MIC can be determined for each isolate. The agar dilution method has been proposed by the Clinical Laboratory Standard Institute (CLSI), as the method to be used for *H. pylori* for clarithromycin susceptibility testing as it is clinically most significant. Other genotyping methods can also be used in detecting resistance against clarithromycin, the most promising technique is probably the real-time PCR based on 23S ribosomal DNA specific

sequence detection. The Maastricht III Consensus Report does not recommend routine metronidazole susceptibility testing.<sup>39</sup>

### Salvage Therapy

Levofloxacin based therapy (levofloxacin 500 mg OD + amoxicillin 1 g BD + PPI BD) can be used in patients who failed eradication with standard triple therapy. Both meta-analyses found that levofloxacin triple therapy was better tolerated than quadruple therapy and had better eradication rates 81% vs. 70%, respectively.<sup>55,56</sup> Ten-day levofloxacin triple therapy was superior to 7-day therapy, and levofloxacin at 250 mg BD was as good as 500 mg BD. Of the 3 salvage therapies described in this section, levofloxacin is the best documented and therefore the preferred therapy. In small trials, Rifabutin has been shown to be effective in eradicating H pylori in patients who have failed traditional therapies. The usual doses in rifabutin triple therapy are rifabutin 150 mg BD, amoxicillin 1 g BD, and a PPI administered twice a day.<sup>57</sup> In one recent study, the eradication rate was 74%. Levofloxacin triple therapy was significantly better than rifabutin triple therapy (85% vs. 45% respectively).<sup>58</sup> Furazolidone-based triple therapy has been shown to be effective in small studies. The usual doses are furazolidone 00–200 mg + amoxicillin 1 g + PPI all administered twice daily for 1 week.<sup>59</sup> In one study, the intent-to-treat eradication rate was 52% in patients who had failed standard therapy. Furazolidone therapies have been less well studied than rifabutin- and levofloxacin-based studies. The low cost of furazolidone makes this regimen particularly attractive in developing countries, but the optimal dose and combination needs further studies.

### Conclusion

H. pylori is sero-epidemiologically proven

aetiological factor involved in acid peptic disease and gastric malignancy. There has been increasing evidence that eradication has definitely reduced the chances of recurrence of gastric and duodenal ulcers and has progression of dysplasia to frank invasive gastric Carcinoma. However, emergence of resistant species of H. pylori against the commonly used triple therapy regimen has lead difficulties in eradication. Uses of new drugs and sequential therapy have shown better outcomes than conventional triple drug therapy.

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#### **BACLOFEN FOR ALCOHOLISM**

Giovanni Addolorato and colleagues report the first randomized placebo-controlled trial of a treatment for alcoholic patients with cirrhosis of the liver. Their finding that baclofen, a GABA<sub>B</sub> receptor agonist, was better than placebo for reduction of drinking in such patients is of interest both because of its specific results and because it highlights the broader context of drug treatment for alcoholism. Addolorato and colleagues' results are surprisingly robust in favour of baclofen, with nearly three-quarters of patients on baclofen maintaining sobriety compared with about a quarter of placebo patients.

The short-term safety of anacetrapib, as found by Krishna and colleagues (which needs to be confirmed in the longer term) opens new perspectives in the study of the effect of CETP inhibition on atherogenesis and cardiovascular risk, and may resuscitate the hope that CETP inhibitors could be an important new class of drugs that normalize lipidaemia.

**Patrick Duriez, The Lancet, 2007; 370 : 1883-84.**