

# *Helicobacter Pylori* and Peptic Ulcer Disease – A Causal Link

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## Summary

The link between *Helicobacter pylori* and peptic ulcer disease in 1997 is an irrefutable one. The association between infection and ulcerogenesis has been shown to be biologically plausible with induction of epithelial inflammation and cell damage and its effect on gastrin/acid homeostasis. The association of *H. pylori* infection and peptic ulcer disease is a close and consistent one. There is ample evidence indicating that *H. pylori* eradication results in virtual abolition of ulcer relapse. Several studies have demonstrated that eradication of *H. pylori* results in ulcer healing and there is evidence showing a temporal relationship between infection and development of peptic ulcer disease.

**Key Words:** *Helicobacter pylori*, Peptic ulcer, Acid secretion, Ulcer healing

## Introduction

A peptic ulcer is defined as a breach in the gastroduodenal mucosa with penetration through the muscularis mucosa and is thought to be due to the action of acid and pepsin in the stomach. Peptic ulcer disease is a chronic relapsing disease, involving usually, the distal part of the stomach and the first part of the duodenum.

Peptic ulcer disease has for a long time, been considered to be a disease of unknown aetiology. Several factors, including genetic factors-blood group O and lack of secretor status and smoking are recognized predisposing factors which may affect gastroduodenal defence or gastric acid/pepsin secretion. The imbalance between gastroduodenal protective mechanisms and acid/pepsin results in ulceration. The emphasis therefore, in the therapeutic approach to peptic ulcers has been to neutralize or to suppress acid-secretion or alternatively to bolster the gastroduodenal mucosal defences with gastroprotective or "mucosally active" agents.

The discovery of *H. pylori* has however, changed dramatically our traditional concept of ulcer pathogenesis. While acid and pepsin continues to play

an important role in causing the breach in gastroduodenal mucosa, *H. pylori* infection has been shown to be the underlying pathogenic mechanism in ulcerogenesis; weakening the gastroduodenal defences and altering somatostatin/gastrin/acid homeostasis. *H. pylori* is now believed to play a critical role in the pathogenesis of peptic ulcer disease. This finding has undoubtedly, an enormous impact on our approach to the treatment of peptic ulcers and important and far-reaching implications to clinical practice.

This review discusses the current evidence linking *H. pylori* to peptic ulcer disease.

## Pathogenetic mechanisms in peptic ulcer disease

*H. pylori* is a true human pathogen. *H. pylori* infection of the stomach is invariably associated with chronic superficial gastritis and eradication of the bacteria results in resolution of the gastritis<sup>1</sup>. Human experiments have demonstrated Koch's postulates in relationship to gastritis<sup>2,3</sup>. Two volunteers swallowed pure cultures of *H. pylori*, developed gastritis and symptoms of acute dyspepsia. The infection was treated with eventual eradication of the bacteria and resolution of gastritis. Similarly, when animals were infected with the bacteria,

gastritis ensued. *H. pylori* is also not found in other types of gastritis such as autoimmune<sup>4</sup>, lymphocytic<sup>5</sup> or bile reflux gastritis<sup>6</sup> indicating that it is not merely a commensal colonizing a damaged mucosa.

*H. pylori* is a highly evolved microorganism which the carved out a unique ecological niche for itself in the human stomach. Its spiral shape and flagella allows it to "swim" and burrow through thick viscid mucus. It induces epithelial damage through a combination of factors: secretion of enzymes including urease, catalase and phospholipases; tight adhesion to the epithelial cells and production of a vacuolating cytotoxin. It evokes a vigorous but largely ineffective immune response. Through all these however, a stable infection develops with a balance existing between the human host and the bacteria allowing the infection to persist if untreated for many years and in all probability for the life-time of the patient<sup>7</sup>.

#### Gastric ulcer

The chronic gastritis found in these patients is a diffuse chronic pangastritis<sup>8</sup>. Glandular atrophy and intestinal metaplasia are frequently present; their extent and severity appears to increase with age<sup>9</sup>. When these changes are extensive, *H. pylori* may not be found in the gastric epithelium which is no longer hospitable to the bacteria. Damage to the mucosa may be due to direct cytotoxic effect or an indirect injury consequent upon immune response. Ulcers will then occur in the face of an attack by acid and pepsin.

#### Duodenal ulcer

The gastritis associated with duodenal ulcers is predominantly confined to the antrum<sup>10,11</sup>. The reason for this is not entirely known but is believed to be because of increased acid secretion which prevents colonization of the acid-producing corpus mucosa. This is important as it spares the parietal cell mass allowing continued acid secretion.

Gastric metaplasia in the duodenal bulb appears to be the key pathological change in duodenal ulcer disease<sup>12</sup>. Gastric metaplasia occurs in response to injurious stimuli; in this case, a high acid load. The occurrence of gastric metaplasia allows colonization of the duodenal mucosa. In the face of acid attack, ulcers form in the weakened mucosa.

#### Acid secretion and duodenal ulcers

There is now consistent evidence that *H. pylori* infection is associated with an increase in both basal and meal stimulated gastrin concentrations<sup>13,14,15,16</sup>. The mechanism by which *H. pylori* stimulates gastrin secretion is not entirely clear. Levi *et al* 1989 *et al* suggested that ammonia produced by *H. pylori* may raise intragastric pH and thereby the preventing physiological negative feedback to gastrin release by intragastric acid. However, increasing intragastric ammonia with infusion of urea or inhibiting bacterial urease activity has not resulted in any change in gastrin levels<sup>17,18</sup>. It is therefore unlikely that hypergastrinaemia is secondary to bacterial ammonia.

The release of gastrin from the gastric antrum is inhibited by somatostatin produced by the antral D-cells. It is postulated that *H. pylori* infection may affect somatostatin levels resulting in a loss of inhibitory control of gastrin release<sup>19</sup>. Mucosal somatostatin has in fact been shown to be depleted in *H. pylori* infected patients but rose significantly after eradication of the infection<sup>20-23</sup>.

While initial studies on acid secretion and *H. pylori* had yielded conflicting results, more recent studies have shown an increased basal and GRP-stimulated acid secretion in both *H. pylori* infected duodenal ulcer and non-duodenal ulcer patients<sup>24</sup>. Although the increase in gastrin concentrations is of about the same magnitude in *H. pylori* positive patients with duodenal ulcers as in those without ulcers, the increase in both basal and stimulated acid secretion in the latter group is significantly higher. The exaggerated acid secretion in duodenal ulcer patients compared to non-ulcer patients can be explained by an increased parietal cell mass in duodenal ulcer patients. This increased parietal cell mass may be the result of long standing trophic effects of *H. pylori* induced hypergastrinaemia or to other factors. Importantly, following successful eradication in duodenal ulcer patients, it has been shown that the increased acid secretion returns to normal with time<sup>25</sup>.

#### Prevalence of *H. Pylori* in peptic ulcer disease

Both duodenal and gastric ulcers are closely associated

with *H. pylori* infection. This association is a consistent one and reported from all over the world. Prevalence rates of >90% have been reported for duodenal ulcers and from 70-90% for gastric ulcers<sup>26</sup>. Local experience in Malaysia is consistent with the above findings; in a large endoscopic cross-sectional survey, *H. pylori* was found in 91.4% (95% CI:86.8,94.7) of duodenal ulcers and 74.1% (95% CI:65.8,82.3) of gastric ulcers<sup>27</sup>.

### *H. Pylori* and peptic ulcer relapse

The strongest and most persuasive evidence for the pathogenic role of *H. pylori* in peptic ulcer disease is the marked reduction or virtual abolition of peptic ulcer relapse following successful *H. pylori* eradication. Peptic ulcer disease, in particular duodenal ulcers is known to be a chronic relapsing disease. Up to 80%

of healed duodenal ulcers will relapse within a year if acid-suppressing maintenance therapy were not prescribed to the patient<sup>28</sup>. The idea that eradication of *H. pylori* would result in lower relapse rates arose from the observations of comparative duodenal ulcer healing studies with bismuth and acid-suppressing agents where the former resulted in significantly lower relapse rates<sup>29</sup>. Coghlan *et al*<sup>30</sup> were the first to attempt eradication therapy and reported lower relapse rates following successful eradication. Subsequent studies, in particular by Rauws and Tytgat<sup>31</sup> has in fact demonstrated that ulcer relapse was abolished with eradication of the bacteria. Forbes *et al*<sup>32</sup> reported on a 7 year follow-up of healed duodenal ulcers and found an ulcer relapse rate of 3% in patients who had eradicated *H. pylori*. A local study<sup>33</sup>, reported a duodenal ulcer relapse rate of only 2.9% following a 24 month follow-up. Table I summarizes the duodenal

**Table I**  
Duodenal ulcer relapse rates in patients with persistent *H. pylori* infection and in patients after eradication of *H. pylori*

Reference	n	Follow up (MO)	Duodenal ulcer relapse (%)	
			<i>H. pylori</i> positive	<i>H. pylori</i> negative
Coghlan <sup>30</sup>	39	12	22/29 (76%)	1/10 (10%)
Marshall <sup>34</sup>	70	12	38/47 (81%)	5/23 (22%)
Smith <sup>35</sup>	36	18	20/29 (69%)	0/7 (0%)
Borody <sup>36</sup>	58	9-37	3/4 (75%)	0/54 (0%)
Rauws <sup>31</sup>	38	12	17/21 (81%)	0/17 (0%)
George <sup>37</sup>	62	12-48	-	0/62 (0%)
Patchett <sup>38</sup>	84	12	18/51 (35.3%)	0/33 (0%)
Fiocca <sup>39</sup>	144	6	55/114 (48%)	3/30 (10%)
Sobala <sup>40</sup>	61	12	25/44 (57%)	1/17 (6%)
Coelho <sup>41</sup>	48	18	10/19(53%)	0/19 (0%)
Bayerdoffer <sup>42</sup>	53	9	12/25 (48%)	0/22 (0%)
Labenz <sup>43</sup>	48	12	14/19 (74%)	1/29 (3%)
Hentschel <sup>44</sup>	104	12	45/53 (85%)	1/46 (2%)
Unge <sup>45</sup>	227	6	52/146 (35.6%)	5/81 (6.3%)
Forbes <sup>32</sup>	64	72-96	5/25 (20%)	1/38 (3%)
Goh <sup>33</sup>	38	24	-	1/35 (2.9%)
Louw <sup>46</sup>	48	24	15/21(71.4%)	5/27 (18%)

ulcer relapse rates in patients with persistent *H.pylori* infection and in those who had eradicated the bacteria. There have been fewer reports on gastric ulcer relapse following *H.pylori* eradication; nonetheless relapse rates have also been shown to be markedly reduced<sup>47,48,49</sup>.

### Ulcer healing with *H.Pylori* eradication

Zheng *et al*<sup>50</sup> reported on the healing of peptic ulcers with antibiotics alone compared to placebo. In a double blind comparative study, furazolidine or placebo was prescribed for 14 days. The ulcer healing rate was significantly higher in the antibiotic treatment arm compared to the placebo arm (73% vs 24%). *H.pylori* status was not determined in this study; it is presumed that ulcer healing is effected following eradication of *H.pylori* in the group that was treated with antibiotics.

Although the eventual ulcer healing rate was similar, Graham *et al*<sup>51</sup> reported accelerated ulcer healing in a group of duodenal ulcer patients who received ranitidine and antibiotics compared to a group receiving ranitidine alone when reviewed endoscopically at several time points (2, 4, 6, 8, 12 and 16 weeks) (Table II). Hosking *et al*<sup>52</sup> and Sung *et al*<sup>53</sup> from Hong Kong, reported two studies on duodenal and gastric ulcer healing respectively and surmised that an effective 1 week *H.pylori* eradication therapy with short course therapy was enough to effect ulcer healing without the need for antacid therapy. However in both their studies, bismuth compounds with possible prolonged effects were used. A more recent report<sup>54</sup> showed that duodenal ulcers continued to heal with short course dual therapy with omeprazole or

famotidine and clarithromycin without the need for continued acid suppressing or ulcer healing agents again indicating the central role of *H.pylori* in ulcer healing (Table III).

**Table III**  
Ulcer healing in *H.pylori* eradicated and not eradicated patients at Week 2 and Week 6

<i>H.pylori</i> status	Ulcer Healing	
	Week 2	Week 6
Eradicated	30/44 (68.2%)	42/44 (95.5%)
Not eradicated	14/19 (73.7%)	7/19 (36.8%)

Goh *et al* 1996<sup>54</sup>

Perhaps, the best study to date and presented recently is from Lam *et al* from Hong Kong<sup>55</sup> where, 81 evaluable patients received a combination of 3 antibiotics for 3 weeks or placebo in a randomized, double-blind fashion. When assessed at 4,8 and 12 weeks, duodenal ulcer healing was significantly better in the antibiotic treated group compared to placebo (92.5%, 100% and 100% vs 36.6%, 61.0% and 63.4% respectively). Using stepwise discriminant analysis, *H.pylori* clearance was the most important determinant of ulcer healing.

### *H.Pylori* infection preceding ulcer formation

Sipponen *et al*<sup>56</sup> followed up a group of volunteers who had no evidence of ulcer disease on endoscopy for 10 years and found that those who had chronic gastritis had a higher incidence of peptic ulcer disease over this period of time (Table IV). Cullen *et al*<sup>57</sup> in a community-based serological study with a mean follow-up period of 18 years showed that the incidence of peptic ulcer disease was 15% in seropositive patients compared to 3% in seronegative patients. Nomura *et al*<sup>58</sup> performed a nested case-control study on a large cohort of Japanese-American men in Hawaii over a surveillance period of more than 20 years and found that 93% of 150 patients with gastric ulcers and 92% of 65 patients with duodenal ulcers had positive *H.pylori* serology compared to 78% of matched controls in both subgroups. The risk of developing both gastric (odds ratio-3.2; 95% C.I.: 1.6-6.5) and

**Table II**  
Ulcer healing in ranitidine treated and ranitidine and triple therapy treated patients

Week	Cumulative % ulcer healed				
	2	4	8	12	16
Ranitidine	18	53	68	80	84
Ranitidine & Triple therapy	37	74	84	96	98

Graham *et al* 1991<sup>51</sup>

**Table IV**  
**Cumulative 10-year risk of symptomatic duodenal and gastric ulcer in patients with or without chronic gastritis**

Histology	n	Ulcer incidence (%)
Normal	133	1 (0.8%)
Gastritis	321	34 (10.6%)

Sipponen *et al* 1990<sup>56</sup>

duodenal (odds ratio-4.0; 95% C.I.: 1.1-14.2) ulcers were significantly increased in *H.pylori* infected individuals.

#### Which *H.Pylori* infected patient develops ulcers?

Although *H.pylori* is frequently found in patients with peptic ulcers, it is estimated that only 16% of *H.pylori* infected patients develop ulcers<sup>26</sup>. The reason for this is not entirely resolved but may depend on both host

factors and virulence factors of the bacteria. Familial clustering of ulcer disease led to search for genetic factors to account for host susceptibility to ulcer development. Twin studies have shown a higher concordance rate for monozygotic compared to dizygotic twins for peptic ulceration<sup>59</sup>. Other host factors include behavioral or environmental factors such as smoking and non-steroidal inflammatory drug ingestion. However, the effect of smoking on peptic ulceration, appears to be nullified when *H.pylori* is eradicated<sup>60,61</sup> and the additional risk with concomitant NSAID ingestion remains unproven<sup>62</sup>. The bacterial virulence factor that has evoked the greatest interest is that of a vacuolating cytotoxin. Several studies have shown that cytotoxin-producing *H.pylori* strains<sup>63,64</sup> and Cag A positive *H.pylori* strains are associated with peptic ulcer disease<sup>65-69</sup>.

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