

## Review Article

# Eradication of *Helicobacter pylori*: therapies and clinical implications

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**Summary:** This review presents a critical evaluation of the role of *Helicobacter pylori* eradication in the management of peptic ulcer disease and non-ulcer dyspepsia. On current evidence, *H. pylori* eradication therapy seems likely to emerge as the most rational and cost-effective treatment for duodenal ulcer. The role of *H. pylori* eradication in the treatment of gastric ulcer and non-ulcer dyspepsia is unclear and requires further study. The emerging problem of antibiotic resistance in *H. pylori* is of major clinical importance and a prime cause of treatment failure. There is increasing evidence of a link between *H. pylori* and gastric cancer but it is premature to recommend large-scale eradication of *H. pylori* as a valid strategy for the primary prevention of gastric cancer. The search continues for the ideal *H. pylori* eradication regimen.

## Introduction

Since Warren and Marshall<sup>1</sup> first described the presence of *Campylobacter*-like organisms (now *Helicobacter pylori*<sup>2</sup>) in the human stomach, there has been phenomenal growth, which continues apace, in the volume of research literature on this microorganism. Several excellent general reviews on *H. pylori* are now available.<sup>3–6</sup> Much recent interest, however, has centered on eradication of infection and this review specifically focuses on the therapies available and the clinical implications of eradication of *H. pylori* in peptic ulcer disease and non-ulcer dyspepsia. The evidence linking *H. pylori* and gastric cancer is also evaluated and the possible future role of *H. pylori* eradication in the primary prevention of gastric cancer is commented on.

## Duodenal ulcer

The early observations by the Perth group<sup>7</sup> that over 95% of duodenal ulcer patients had *H. pylori* infection and that the ulcer-healing agent colloidal bismuth subcitrate (CBS) was helicobactericidal provoked detailed re-evaluation of the role of bismuth and antibiotics in the treatment of duodenal ulcer disease. The fact that CBS was as effective as cimetidine or ranitidine in healing ulcers and somehow prevented ulcer relapse was already

well known though ill understood.<sup>8–10</sup> Further interest was generated by early reports that furazolidone<sup>11</sup> and metronidazole,<sup>12</sup> both active against *H. pylori*, were as effective as H<sub>2</sub> blockers in healing duodenal ulcer.

Our understanding of both the pathogenic role of *H. pylori* and of the mode of action of bismuth in duodenal ulcer took a major step forward with publication of the landmark study of Coghlan *et al.*<sup>13</sup> In this single-blind trial, 66 patients were randomized to 6 weeks therapy with either CBS (DeNol) liquid (120 mg four times a day) or cimetidine (400 mg twice a day). Healing rates were similar in the two groups but over a 12 month follow-up period, ulcer relapse occurred in 79% of patients who remained *H. pylori*-positive after treatment compared with only 27% of those rendered *H. pylori*-negative. Histological gastritis was universal in the *H. pylori*-positive group but absent in the *H. pylori*-negative group. Only post-treatment *H. pylori* status was a significant predictor of ulcer relapse. In a reply to Coghlan's paper, Bianchi Porro and Lazzaroni<sup>14</sup> reported that they were unable to demonstrate *H. pylori* as a risk factor for duodenal ulcer recurrence but this was a small uncontrolled study with only a 6 month follow-up period during which one patient group continued on maintenance H<sub>2</sub> blocker therapy that may have prevented ulcer relapse in *H. pylori*-positive patients. Furthermore, several subsequent studies<sup>15–20</sup> have confirmed Coghlan's findings (Table I).

In the study by Marshall *et al.*<sup>16</sup> 100 *H. pylori*-

**Table 1** *H. pylori* eradication and duodenal ulcer relapse

Study	Treatment	Patients n	Follow-up duration (months)	Ulcer relapse	
				HP + ve	HP - ve
Coghlan <i>et al.</i> (1987) <sup>13*</sup>	CBS vs CIM	40	12	19/25 (79%)	4/15 (27%)
Lambert <i>et al.</i> (1987) <sup>15</sup>	CBS	20	6	8/8 (100%)	NS
Marshall <i>et al.</i> (1988) <sup>16</sup>	CBS vs CBS + TIN	68	12	37/44 (84%)	5/24 (21%)
	vs CIM vs CIM + TIN				
Smith <i>et al.</i> (1988) <sup>17</sup>	CBS vs RAN	44	18	18/22 (82%)	7/22 (32%)
Fiocca <i>et al.</i> (1991) <sup>19</sup>	CBS vs CBS + AMOX	144	6	55/114 (48%)	3/30 (10%)
	vs RAN vs RAN + AMOX				
Lamouliatte <i>et al.</i> (1991) <sup>20</sup>	OM + AMOX	44	12	15/18 (83%)	1/26 (4%)
	vs OM + AMOX + TIN				
	vs RAN + AMOX + TIN				

\*Reference; AMOX = amoxicillin; CBS = colloidal bismuth subcitrate; CIM = cimetidine; HP = *H. pylori*; NS = not stated; OM = omeprazole; RAN = ranitidine; TIN = tinidazole; + ve = positive; - ve = negative.

positive duodenal ulcer patients were randomized to 8 weeks therapy with either cimetidine or CBS tablets with tinidazole or placebo administered concurrently for the first 10 days of treatment. Of the patients who remained *H. pylori*-positive after therapy, only 61% of ulcers healed and 84% relapsed over the 12 month follow-up period, whereas 92% of ulcers healed and only 21% relapsed in the patients *H. pylori*-negative after therapy. The highest eradication rate was achieved in the group who received dual therapy with CBS and tinidazole. Sex, age, smoking and history of previous ulcer had no significant effect on relapse provided *H. pylori* had been eradicated. It is noteworthy, however, that over 20% of ulcers relapsed despite *H. pylori* eradication, implying that factors other than *H. pylori* are involved in duodenal ulcer relapse.

Two recent studies<sup>21,22</sup> have gone further and claimed cure of duodenal ulcer after eradication of *H. pylori*. Both studies recruited *H. pylori*-positive patients with troublesome ulcer disease (break-through despite maintenance H<sub>2</sub> blocker therapy or frequent relapse) who were openly prescribed triple therapy with CBS, metronidazole and either amoxicillin<sup>21</sup> or tetracycline.<sup>22</sup> Ulcer relapse was not seen in *H. pylori*-negative patients in either study including a 4 year follow-up by the Australian group.<sup>22</sup> Despite these impressive results use of the term 'cure' may be premature, particularly in view of the relapsing nature of ulcer disease,<sup>23</sup> the relatively short follow-up period, and the potential for reinfection with *H. pylori*.<sup>24</sup> Both studies again support a dominant role for *H. pylori* in duodenal ulcer recurrence and also suggest that the lower relapse rate seen after CBS therapy<sup>8-10</sup> predominantly results from the antibacterial action of the drug<sup>25</sup> rather than its cytoprotective properties<sup>26</sup> or a 'depot' effect after absorption.<sup>27</sup>

## Clinical implications

### Choice of treatment in duodenal ulcer

Histamine H<sub>2</sub> blockers offer safe, rapid symptom relief and healing in duodenal ulcer.<sup>28</sup> Their Achilles heel, however, is ulcer relapse which occurs in up to 90% of patients within a year after discontinuing therapy.<sup>29,30</sup> On present evidence, eradication of *H. pylori* offers a clear opportunity to prevent ulcer relapse and effectively alter the natural history of the disease. Thus, should all duodenal ulcer patients with *H. pylori* infection now receive eradication therapy?

Some gastroenterologists would say 'yes' in view of the chronicity of the disease and the potential for relapse and complications. On the other hand, patients who suffer a mild symptomatic relapse once or twice a year, which is easily controlled by a short course of H<sub>2</sub> blocker therapy, seem unlikely to benefit much from *H. pylori* eradication therapy. In contrast, patients who suffer frequent troublesome ulcer relapse and need continuous H<sub>2</sub> blocker therapy or are being considered for ulcer surgery should be offered an effective eradication regimen such as CBS 120 mg four times a day for 4 weeks with metronidazole 400 mg and tetracycline 500 mg both three times a day for the first week of therapy.<sup>31-33</sup> Logan *et al.*<sup>34</sup> have recently described a short one-week regimen consisting of CBS 120 mg and amoxicillin 500 mg both four times a day for 7 days with metronidazole 400 mg five times daily for 3 days which gave an overall eradication rate of 72%, increasing to 93% in patients with metronidazole-sensitive *H. pylori*. The potential impact of *H. pylori* therapy in the prevention of ulcer haemorrhage and perforation remains to be assessed, though George *et al.*<sup>22</sup>

provide anecdotal evidence of a possible beneficial effect.

#### Antibiotic resistance

As clinical experience with *H. pylori* eradication increases, it has become clear that the problem of *H. pylori* antibiotic resistance, and particularly nitroimidazole resistance, is of major importance. The widespread adoption of the nitroimidazoles, and especially metronidazole, in eradication regimens owes much to the early eradication studies of Marshall and colleagues,<sup>35</sup> and the fact that metronidazole is both bactericidal at low pH<sup>36</sup> and present in high concentration in gastric juice.<sup>37</sup> Ironically, the Perth group also highlighted the problem of antibiotic resistance when tinidazole-resistant *H. pylori* emerged in the course of their duodenal ulcer relapse study<sup>16</sup> in nearly all patients not receiving concurrent CBS therapy. Goodwin *et al.*<sup>38</sup> subsequently showed that nitroimidazole resistance could be prevented by coadministration of CBS.

More recent studies have shown a strong association between primary nitroimidazole resistance in *H. pylori* and both previous administration of these agents for unrelated reasons<sup>39</sup> (vaginal infections, amoebiasis, giardiasis, perioperative prophylaxis in uterine and colonic surgery) and ethnic origin.<sup>40</sup> The rate of primary resistance to metronidazole among native-born Belgians was only 17% compared with 84% in adults from Zaire.<sup>40</sup> It is also clear that routine metronidazole-sensitivity testing of *H. pylori* cultured from antral biopsies can predict treatment outcome. Weil *et al.*<sup>41</sup> using dual-therapy metronidazole and CBS achieved an 85% eradication rate in patients with metronidazole-sensitive isolates compared with only 14% in patients with metronidazole-resistant *H. pylori*. In effect, eradication regimens incorporating nitroimidazoles are unable to eradicate *H. pylori* in cases of primary nitroimidazole resistance, and treatment failure in nitroimidazole-sensitive strains may induce secondary resistance. These data further emphasize that comparisons of treatment schedules for *H. pylori* infection should ideally be done in patient groups where the level of antibiotic resistance is similar. Fears have also been expressed<sup>33</sup> that indiscriminate use of *H. pylori* therapy might promote the emergence of 'super-resistant' bacteria and paradoxically increase the problems of eradication in the future.

Finally, current treatment options for nitroimidazole-resistant *H. pylori* are limited but Logan *et al.*<sup>42</sup> have devised a 2-week eradication regimen consisting of omeprazole 40 mg mane and amoxicillin 500 mg four times a day for 2 weeks, with CBS 120 mg four times a day for days 1–7, and ciprofloxacin 750 mg twice daily for days 7–14

which gave an eradication rate of 74% in patients with known metronidazole-resistant *H. pylori*.

#### Omeprazole

Omeprazole is a potent inhibitor of gastric acid secretion which exerts its effect by inactivating the H<sup>+</sup>/K<sup>+</sup> + ATPase enzyme system in the parietal cell canaliculus after proton-dependent activation of the prodrug.<sup>43</sup> Omeprazole and other substituted benzimidazoles (pantoprazole and lansoprazole) are active against *H. pylori in vitro*.<sup>44,45</sup> This finding and early reports that omeprazole was effective in eradicating *H. pylori in vivo*<sup>46,47</sup> generated considerable interest. More rigorous long-term evaluation, however, has shown that omeprazole *per se* causes suppression but not eradication of *H. pylori in vivo*.<sup>48,49</sup> On the premise that omeprazole-induced hypochlorhydria might prevent acid inactivation of antibiotics used to eradicate *H. pylori*, omeprazole has also been evaluated in dual and triple therapy regimens. For instance, preliminary studies of an amoxicillin-omeprazole regimen<sup>50</sup> achieved a 67% eradication rate compared with 85% for an omeprazole–amoxicillin–tinidazole combination<sup>51</sup> and 50% for combination omeprazole–CBS–erythromycin.<sup>52</sup>

#### Gastric ulcer

The association between *H. pylori* and peptic ulcer disease is stronger for duodenal than for gastric ulceration, in that virtually all duodenal ulcer patients have *H. pylori*-positive antral gastritis whereas about 30% of gastric ulcer patients are consistently *H. pylori*-negative.<sup>53</sup> This finding coupled with the relative rarity of gastric compared with duodenal ulcer may account for the dearth of data on the effects of *H. pylori* eradication in gastric ulcer.

In a study of 43 *H. pylori*-positive gastric ulcer patients randomized to receive 12 weeks treatment with either cimetidine or cimetidine plus cefixime in the last 2 weeks of therapy, Tatsutu *et al.*<sup>54</sup> found a similar healing rate in the two groups but a significantly lower recurrence rate at 12 weeks after finishing treatment in the dual therapy group; ulcer recurrence was, however, similar in the two groups at 24 weeks. Clearly, further studies of *H. pylori* eradication in gastric ulcer are needed which will incorporate large patient numbers, more effective eradication regimens and longer follow-up.

#### Socioeconomic impact of *H. pylori* eradication

The socioeconomic costs of peptic ulcer disease are very high. Firstly, peptic ulcer disease is a common

condition which affects between 1 and 2% of adults in Western society annually and carries a lifetime prevalence in the population of about 10%.<sup>55</sup> Secondly, peptic ulcer is a chronic disorder, characterized by frequent recurrences which may be complicated by life-threatening bleeding or perforation. The direct costs of peptic ulcer disease include consultations, diagnostic tests, hospitalization and drug therapy, whereas the indirect costs include absenteeism, poor work performance and quality of life and possible death from complications.<sup>56</sup> Continuous maintenance H<sub>2</sub> blocker therapy is cost-effective for peptic ulcer largely by reducing direct medical costs<sup>57</sup> but entails considerable cumulative expense for the patient over several years.

Though they have not yet been directly compared in a controlled clinical trial, current evidence suggests that effective *H. pylori* eradication therapy gives an ulcer relapse rate at least as low as maintenance H<sub>2</sub> blocker therapy. Thus, by minimizing direct and indirect costs without the need for expensive maintenance therapy, it seems likely that *H. pylori* eradication therapy may prove the most cost-effective treatment for peptic ulcer.<sup>58</sup>

### Non-ulcer dyspepsia

The term dyspepsia refers to chronic or recurrent upper abdominal symptoms (pain, discomfort, nausea, flatulence, bloating, heartburn), often related to eating, which raise the possibility of peptic ulcer disease.<sup>59</sup> On investigation, about a third of patients will be shown to have a peptic ulcer, a third various other diagnoses such as gallstones and irritable bowel syndrome, and the remainder will have no obvious abnormality, i.e. have non-ulcer dyspepsia (NUD).<sup>60</sup>

The pathogenesis of NUD remains unknown with inconclusive evidence for several factors including gastric acid secretion,<sup>59</sup> abnormal gastro-

duodenal motility,<sup>61</sup> duodenogastric reflux,<sup>62,63</sup> gastrointestinal peptide hormones,<sup>64</sup> personality traits,<sup>65</sup> and stress.<sup>66</sup> The relationship between *H. pylori* and NUD is controversial. The reported prevalence of *H. pylori*-associated gastritis in NUD ranges from 39%<sup>67</sup> to 87%<sup>68</sup> but it remains unclear whether *H. pylori* infection *per se* causes chronic dyspeptic symptoms.<sup>7,69-71</sup> A typical clinical syndrome for *H. pylori* infection has not been identified,<sup>72</sup> the infection occurs in healthy asymptomatic individuals,<sup>73</sup> and voluntary<sup>74</sup> or inadvertent<sup>75</sup> ingestion of *H. pylori* causes only a short-lived dyspeptic illness.

Controlled studies of *H. pylori* therapy in NUD have yielded conflicting results (Table II). Of six placebo-controlled trials of bismuth in the treatment of NUD,<sup>67,76-80</sup> three<sup>67,77,80</sup> reported significant clinical improvement associated with clearance of *H. pylori*. In placebo-controlled trials of antibiotics in NUD, Ponderoux *et al.*<sup>81</sup> found that amoxycillin improved symptoms associated with clearance of *H. pylori* and resolution of gastritis whereas Patchett *et al.*<sup>82</sup> found no correlation between eradication of *H. pylori* and short-term symptomatic improvement. Relatively small study populations coupled with differences in definition of NUD and thus in inclusion/exclusion criteria may account for some of these disparate results, and all but one of the studies<sup>82</sup> assessed clearance rather than eradication. In an interesting one year follow-up of the patients studied by Patchett *et al.*<sup>82</sup> it is noteworthy that dyspepsia scores in patients with persistent *H. pylori* infection were significantly higher than in patients remaining free of infection, suggesting that eradication of *H. pylori* in NUD may produce beneficial long-term effects.<sup>83</sup> At present, pending further data, *H. pylori* therapy in NUD should ideally remain within the confines of a controlled clinical trial.

Table II *H. pylori* eradication in non-ulcer dyspepsia

Study	Treatment	Patients n	HP + ve n (%)	Follow-up duration (weeks)	Symptomatic improvement with HP clearance
McNulty <i>et al.</i> (1986) <sup>76</sup>	BS vs EE vs placebo	50	50 (100)	3	No
Rokkas <i>et al.</i> (1988) <sup>67</sup>	CBS vs placebo	52	20 (39)	8	Yes
Loffeld <i>et al.</i> (1989) <sup>78</sup>	CBS vs placebo	50	50 (100)	8	No
Lambert <i>et al.</i> (1989) <sup>77</sup>	CBS vs placebo	82	50 (61)	4	Yes
Kang <i>et al.</i> (1990) <sup>79</sup>	CBS vs placebo	51	20 (39)	8	No
Vaira <i>et al.</i> (1991) <sup>80</sup>	CBS vs placebo	80	80 (100)	NS	Yes

\*Reference; BS = bismuth salicylate; CBS = colloidal bismuth subcitrate; EE = erythromycin ethylsuccinate; HP = *H. pylori*; NS = not stated; + ve = positive.

## Gastric cancer

There is growing evidence of a link between *H. pylori* infection and gastric cancer.<sup>84</sup> Gastric cancer almost always develops on a background of chronic gastritis<sup>85</sup> and *H. pylori* is now increasingly recognized as the cause of type B chronic gastritis,<sup>86</sup> the predominantly antral form of chronic gastritis which is by far the commonest form worldwide.<sup>87</sup> There are close parallels between the epidemiology of *H. pylori* infection and gastric cancer. In areas of high prevalence for both gastric cancer and chronic gastritis, *H. pylori* infection is commonly acquired in childhood<sup>88,89</sup> whereas this is rare in countries such as North America with a low prevalence of gastric cancer.<sup>90</sup> There is a strong association between gastric cancer risk and overcrowding in the home during childhood which might act by promoting the transmission of *H. pylori* infection.<sup>91</sup> The frequency of *H. pylori* infection is increased in subjects from the lower social classes,<sup>92,93</sup> who are also known to have a significantly higher prevalence of gastric cancer.<sup>94</sup>

Serological studies in rural China have shown a significant geographical correlation between gastric cancer mortality and the prevalence of antibody to *H. pylori*.<sup>95</sup> Furthermore, three recent independent case-control studies<sup>96-98</sup> found that infection with *H. pylori* was associated with an increased risk of gastric cancer. Parsonnet *et al.*<sup>97</sup> found that persons seropositive for *H. pylori* were approximately three times more likely to develop gastric cancer in the ensuing years of follow-up than were control subjects matched for age, sex and race. Nomura *et al.*<sup>98</sup> also showed that as the level of antibody to *H. pylori* increased, there was a progressive increase in the risk of gastric cancer.

Vitamin C is both a potent antioxidant and an effective scavenger of nitrite, reducing it to nitric oxide and preventing N-nitroso compound formation *in vitro*<sup>99</sup> and *in vivo*.<sup>100</sup> N-nitroso compounds, formed by the interaction of nitrite and nitrosatable substrates, are powerful carcinogens which may well play a key role in the initiation of gastric cancer.<sup>101</sup> Gastric levels of vitamin C are substantially lower in patients with type B chronic gastritis.<sup>102-104</sup> Also, gastric secretory studies,<sup>102,105</sup> including detailed studies in a normal subject who inadvertently contracted *H. pylori* infection,<sup>106</sup> suggest that vitamin C is secreted by the stomach and that secretory capacity is impaired in the presence of gastritis. Hence, *H. pylori* infection may diminish the antioxidant and nitrite-scavenging capacity of gastric juice, thereby increasing the potential for N-nitroso compound formation in the stomach.

Acid secretion diminishes when type B gastritis extends to involve the body of the stomach.<sup>107</sup> Resultant hypochlorhydria leads to bacterial over-

growth and a rise in gastric juice nitrite due to reduction of salivary and dietary nitrate by nitrate-reductase active bacteria.<sup>108,109</sup> This in turn leads to increased levels of N-nitroso compounds in the gastric juice of some hypochlorhydric subjects compared with controls.<sup>110</sup>

Given this setting of enhanced potential for DNA damage, the increased cell turnover and mucosal instability inherent in chronic gastritis,<sup>111</sup> and the known chronicity of *H. pylori* infection, it is conceivable that a series of mutations could occur causing progressive mucosal dedifferentiation from complete to incomplete intestinal metaplasia<sup>112,113</sup> and on to gastric dysplasia. Progression to invasive gastric cancer may ultimately hinge on individual susceptibility factors such as gender,<sup>114</sup> blood group,<sup>115</sup> oncogenes,<sup>116</sup> DNA repair capacity,<sup>117</sup> or cellular concentrations of thiols.<sup>118</sup>

Current strategies for the primary prevention of gastric cancer focus on reducing human exposure to N-nitroso compounds by controlling levels of nitrate in drinking water and foodstuffs. If, however, the *H. pylori*-gastric cancer hypothesis holds true and *H. pylori* is shown to play a pivotal role in the pathogenesis of gastric cancer, eradication of infection could become a prime target for cancer prevention. On present evidence, populations with a high incidence of gastric cancer who acquire *H. pylori* infection early in life would probably benefit most from screening for infection and subsequent eradication.

## Conclusions

In the 10 years since its rediscovery, *H. pylori* has established itself as a major contributory factor in the aetiology of peptic ulcer disease.<sup>3-6,119</sup> Eradication of *H. pylori* in duodenal ulcer dramatically alters the relapsing nature of the disease and an effective helicobactericidal regimen now seems the most rational and cost-effective treatment. The role of *H. pylori* eradication in the treatment of both gastric ulcer and NUD is unclear and requires further evaluation. Systematic follow-up of patients given *H. pylori* eradication therapy is essential to provide accurate long-term data on the critical issues of reinfection and peptic ulcer recurrence. The emerging problem of antibiotic resistance is of major clinical importance and is both a prime cause of treatment failure and a potent reason why random speculative *H. pylori* therapy should be discouraged. Although the link between *H. pylori* and gastric cancer is supported by attractive circumstantial evidence, it is still premature to recommend a large-scale population-based *H. pylori* eradication programme as a valid strategy for the primary prevention of gastric cancer.

The search continues for the ideal *H. pylori*

eradication regimen. Current multi-drug regimens do not offer 100% eradication, are ineffective against antibiotic-resistant *H. pylori*, discourage patient compliance, may encourage secondary antibiotic resistance and are potentially toxic. The ideal therapeutic agent should have a bactericidal mode of action, including efficacy against quiescent coccoid forms of *H. pylori*, possess both topical and systemic activity, be effective across a wide pH range, and be well tolerated and cheap. The

worldwide potential benefits of *H. pylori* eradication in the management of gastroduodenal disease will no doubt stimulate continued research in this important area.

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