Gut 1996; **39:** 781–783

Gut

Leading article

Treating *Helicobacter pylori* – the best is yet to come?

Introduction

In 1983 Warren and Marshall[1] successfully cultured *Helicobacter pylori* from the stomachs of patients with chronic gastritis. Their discovery has revolutionised our understanding of the pathogenesis and treatment of peptic ulcer disease. Yet despite the passage of 13 years and over 700 publications on eradication therapy, consensus on the optimum treatment for *H pylori* infection remains elusive.

Antibacterial treatment of *H pylori* is difficult because of the habitat occupied by the organism below the layer of mucus adherent to the gastric mucosa. It is also difficult because of resistance to antimicrobial agents, especially to nitroimidazoles and increasingly to macrolides, which develops rapidly during treatment, or pre-exists in the community.[2] These factors have led to the concurrent use of several drugs, as exemplified by triple or quadruple regimens. Although these are effective, poor compliance with somewhat complex treatment schedules and adverse effects of the drugs, lessen their efficacy.[3 4]

In 1991 a working party at the World Congress of Gastroenterology in Sydney recommended a triple therapy regimen ('classical' triple therapy) containing bismuth, tetracycline or amoxycillin, and metronidazole: all drugs taken four times daily for two weeks.[5] The efficacy of this treatment is highly dependent on the compliance of the patient and the prevalence of pre-treatment metronidazole resistant strains (MRS) of *H pylori*.[6] Classic triple therapy was successful in 90% of patients with pre-treatment metronidazole sensitive strains (MSS), but in only 30% of patients with MRS, of *H pylori*.[6]

The combination of omeprazole with either amoxycillin or clarithromycin has been a popular alternative to classic triple therapy, but the reported efficacy of these regimens varies widely,[7] and has only moderate efficacy (<80% eradication) in randomised, controlled trials.[8–10] The two week combination of ranitidine bismuth citrate (400 mg twice daily) and clarithromycin (250 mg four times daily) has been reported to eradicate up to 80% of *H pylori* using an intent to treat analysis.[11] Further studies are awaited using shorter less frequent courses and doses of antimicrobials.

Quadruple regimen consisting of omeprazole 20 mg twice daily (for 10 days), with colloidal bismuth subcitrate 120 mg four times daily, tetracycline 500 mg four times daily and metronidazole 500 mg thrice daily for seven days was reported to eradicate 98% of *H pylori* infection.[12] The prevalence of pre-treatment MRS of *H pylori* was only 7·7%. Further studies using this complicated regimen are needed in areas with a high prevalence of MRS of *H pylori*.

Three years ago Bazzoli and colleagues[13] reported 100% *H pylori* eradication in 36 patients using one week, low dose triple therapy regimen containing omeprazole 20 mg once daily, clarithromycin 250 mg and tinidazole 500 mg, twice daily. This regimen was associated with good patient compliance and a low incidence of side effects. Subsequent studies confirmed the efficacy of one week, twice daily combinations of a proton pump inhibitor, clarithromycin and either amoxycillin, or a nitroimidazole (metronidazole or tinidazole); *H pylori* eradication was reported in 85–95% of patients.[14–17] However, most of these studies were small (<75 subjects), not randomised, controlled or comparative, and few reported pre-treatment antimicrobial sensitivities of *H pylori* – important for the determination of efficacy of a treatment containing a nitroimidazole or clarithromycin.

Recent developments

Two large studies of one week, twice daily *H pylori* eradication regimens were published within the last year.[18 19] The MACH 1 study was a European multicentre, double blind, randomised, placebo controlled trial in 723 *H pylori* positive patients with duodenal ulcer.[18] Pre-treatment *H pylori* sensitivities to metronidazole or clarithromycin were not reported. Treatment consisted of omeprazole 20 mg in combination with either placebo, or with two antimicrobial agents twice daily: metronidazole 400 mg, amoxycillin 1 g, and clarithromycin 250 mg or 500 mg; all tablets taken twice daily for one week. Table I shows intent to treat results. The results are very impressive, but it is not possible to ascertain whether the high *H pylori* eradication using OMC250 and OCM500 is attainable in areas with high prevalence of pre-treatment of MRS of *H pylori*.

TABLE I *MACH 1 trial results*[18]

Treatment	H pylori *eradication (n) (%)**
OAC500	106/117 (91)
OAC250	93/117 (79·5)
OMC500	106/124 (85·5)
OMC250	105/117 (90)
OAM	94/124 (76)
OP	1/119 (1)

*Intent to treat analysis. O=omeprazole 20 mg twice daily; A=amoxycillin 1 g twice daily; C500=clarithromycin 500 mg twice daily; C250=clarithromycin 250 mg twice daily; M=metronidazole 400 mg twice daily; P=placebo.

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TABLE II *UK and Eire study*[19]

Treatment	*LAC*	*LCM*	*LAM*	*OAM*
H pylori eradication* n/n (%)	104/121 (86)	103/118 (87)	87/131 (66)	94/126 (75)

*Intention to treat analysis. L=lansoprazole 30 mg twice daily; O=omeprazole 20 mg twice daily; A=amoxycillin 1 g twice daily; M=metronidazole 400 mg twice daily; C=clarithromycin 250 mg twice daily.

The second study, a UK and Eire multicentre, randomised trial, involved 496 *H pylori* positive patients with duodenal ulcer or non-ulcer gastritis.[19] Patients were randomised to either lansoprazole 30 mg plus two of clarithromycin 250 mg, amoxycillin 1 g, metronidazole 400 mg, or to omeprazole 20 mg plus amoxycillin 1 g and metronidazole 400 mg; all given twice daily for one week. Table II shows the results according to an intent to treat analysis.

These two large randomised comparative trials suggest that a one week, low dose twice daily triple therapy regimen containing a proton pump inhibitor with clarithromycin 250–500 mg and either amoxycillin 1 g or metronidazole 400 mg, will cure *H pylori* infection in about 90% of patients.

Effect of metronidazole resistance

In the UK and Eire multicentre study pre-treatment *H pylori* antimicrobial sensitivities were determined on culture of gastric biopsy specimens. The three metronidazole containing regimens were similarly effective in patients with pre-treatment MSS strains of *H pylori*, but were significantly ($p<0.05$) less effective against MRS of *H pylori* (Table III). MRS of *H pylori* may reach 90% prevalence in inner city areas,[2] and there metronidazole containing regimens may be less effective. In such circumstances an eradication regimen comprising a proton pump inhibitor, clarithromycin and amoxycillin may be preferable, as prevalance of pre-treatment clarithromycin resistance in the UK is less than 3%.[19] However, in France the prevalence of clarithromycin resistance may be as high as 17%,[20] and there further studies are needed to clarify the situation.

Interestingly, the importance of metronidazole resistance as a major factor in determining the outcome of eradication regimens for *H pylori* is perhaps not as clear as the UK and Eire multicentre trial suggests.[19] Two recent studies have not shown any effect of metronidazole resistance on the success of treatment with regimens that include metronidazole.[21 22] One study used the lansoprazole, clarithromycin, metronidazole regimen, but the dose of lansoprazole was 30 mg daily.[21] In another trial pre-treatment metronidazole sensitivities of *H pylori* had apparently no effect on the outcome of twice daily treatment with omeprazole, clarithromycin, and metronidazole, or with bismuth subcitrate, clarithromycin, and metronidazole.[22] The conflicting data on the importance of MRS cannot be resolved at present, and further large scale trials will be needed to provide an answer.

TABLE III H pylori *eradication according to pre-treatment metronidazole sensitivities*[19]

Metronidazole sensitivity	*LAC*	*LCM*	*LAM*	*OAM*
H pylori eradication in MSS (%)	54/61 (89)	69/73 (95)	57/63 (91)	60/64 (94)
H pylori eradication in MRS (%)	36/39 (92)	19/25 (76)	18/39 (46)	19/28 (68)

MSS=pre-treatment metronidazole sensitive strains of *H pylori*; MRS=pre-treatment metronidazole resistant strains of *H pylori*.

Future trends

Is it now possible to improve on these results, without compromising patient compliance, or increasing the incidence of side effects? Two recent studies suggest that seven days treatment with low dose triple therapy regimens may be suboptimal, and that 10 day course leads to higher *H pylori* eradication.[22 23] Lerang *et al*[22] in a multicentre, randomised, double blind study reported *H pylori* eradication in 72 of 76 (95%, intent to treat) patients treated for 10 days with twice daily omeprazole 20 mg, clarithromycin 250 mg, and metronidazole 400 mg. The efficacy of this 10 day regimen was unaffected by the pre-treatment metronidazole sensitivity of *H pylori*, with eradication in 17 of 18 (94%) patients with MRS of *H pylori*. This suggests that the increased duration of treatment may overcome metronidazole resistance. Another smaller, but randomised trial, comparing 7, 10 or 14 day triple therapy regimen comprising omeprazole 20 mg, clarithromycin 500 mg, and amoxycillin 1 g twice daily, reported that *H pylori* eradication was significantly ($p<0.05$) higher (83%) with the 10 day, than with the seven day (77%) regimen.[23] Further studies are necessary to determine whether 10 day, low dose triple therapy regimen is the best treatment for *H pylori* infection.

Conclusion

The original guidelines[5] setting out indications for anti-*Helicobacter* treatment have so far stood the test of time – only patients with non-NSAID related duodenal or gastric ulcers should receive eradication therapy. Until recently, neither the primary care physicians, nor even gastroenterologists could take advice from guidelines on which treatment regimen to use, or how to manage the often occurring problems other than simple duodenal ulcer, or gastric ulcer. This unsatisfactory state of affairs is now being remedied, as several National Societies have, or are producing guidelines. Moreover, proceedings of a recent meeting in Maastricht at which most European countries were represented, by gastroenterologists and/or primary care physicians, will shortly be published, with advice on regimens and indications for eradication therapy (Malfertheiner *et al*, personal communication).

It is clear that in the real world indications for *H pylori* treatment are being broadened, and it is impossible to turn back the tide of prescribing by primary care physicians, or gastroenterologists. The guidelines endorse current practice. Many gastroenterologists are reluctant to withold biopsy, even if the stomach is normal macroscopically. If *H pylori* infection is diagnosed in a patient with functional dyspepsia, it is difficult to withhold eradication therapy on the grounds that the superficial gastritis will do no harm. It most probably will not, but absolute reassurance would not be truthful. Many physicians will offer eradication treatment to patients on, or about to, embark on NSAIDs, even though formal evidence of efficacy is not available. Reports of increased incidence of atrophic gastritis on long term proton pump inhibitors given for gastro-oesophageal reflux disease need to be confirmed,[24] before being accepted as a definite indication for *H pylori* therapy. Early gastric cancer, family history of gastric cancer, or the presence of gastric mucosal abnormalities such as intestinal metaplasia, dysplasia, giant rugal hypertrophy, or erosive gastritis, may also prompt the treatment of *H pylori*. MALT lymphoma is probably best treated in specialised units. In the face of such clinical decisions the best course of action is to ensure that the most effective regimen is being prescribed, so that the risk of emergence of resistant strains of *H pylori* is minimised. Further developments in the routine detection of pathogenic strains of *H pylori* will

help to develop appropriate management strategies in individual patients.

At present, one week, twice daily dose, proton pump inhibitor based triple regimens that comprise a proton pump inhibitor, and two of clarithromycin, a nitromimidazole, or amoxycillin, are being recommended in national and European guidelines. Details of dose still remain to be settled with respect to some of these agents, but these regimens are the current best buy. Direct comparisons of different regimens are very important, but will be difficult to realise, given the constraints of prevailing funding sources. Efficacy is important, but must be judged in conjunction with other factors, such as ease of compliance, effectiveness against MRS of *H pylori*, and cost. The available evidence shows that a number of regimens give very similar results, and that suspected or confirmed resistance to nitroimidazoles may, or may not, affect the choice of antimicrobial agents, and perhaps also of the length of treatment. There is still no agreement on whether acid suppression should be continued for a period in all patients after eradication treatment. Perhaps editors of medical journals should attempt to lessen the confusion by carefully considering accretions to the literature pertaining to the treatment of *H pylori*, and publishing only well designed and large trials.

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