The European meeting on Helicobacter pylori: therapeutic news from Lisbon

U Peitz, M Menegatti, D Vaira, P Malfertheiner

Summary
The current standard of Helicobacter pylori treatment has been confirmed by the studies presented at the Lisbon workshop—that is, one of three one week proton pump inhibitor (PPI) based triple therapies comprising a twice daily standard dose of a PPI in combination with two of the following antimicrobial agents: clarithromycin, amoxycillin, or a nitroimidazole. This standard of treatment is also highly efficacious and cost-effective in routine community practice. The current data confirm the equivalence of ranitidine bismuth citrate to PPI, and of azithromycin to clarithromycin. The optimum dose for azithromycin has not yet been defined. There is some evidence that in certain regions treatment for more than one week may be advantageous. The reasons are still not clear. However, microbial resistance may be one important factor, as it has a substantial effect on treatment outcome and the prevalence of resistance varies considerably in different areas. The negative impact of resistance is increased by shortening the treatment time. At present, there is no general necessity to test for resistance before treatment. However, before selection of a second line treatment, testing for resistance is recommended.

Introduction
With the advent of proton pump inhibitor (PPI) based triple therapies initiated by Bell et al and Bazzoli et al, a new standard of Helicobacter pylori treatment efficacy has been set. This has been recently integrated into the recommendations of the Maastricht Consensus Report 1996. On 12–14 September 1997, Lisbon hosted the Xth International Workshop on Gastroduodenal Pathology and Helicobacter pylori, the official international meeting of the European Helicobacter pylori Study Group. A section of this meeting has traditionally been devoted to therapy, and this year it comprised 67 accepted abstracts.

Abstracts addressing the following issues are reviewed. Are any alterations of the dosage, the duration or the number of agents able to optimise the current standard? Is the application of the standard in routine practice as efficacious as in scientific studies and is it cost-effective? What are the predictors of treatment success? Emphasis is placed on microbial resistance which leads to the issue of second line treatment.

Forty two abstracts presented original data on therapeutic trials with 54 treatment arms. The results of seven day treatment arms grouped for the main combinations of antimicrobial agents are given in figures 1–3.

Is more better?

DOSE OF MACROLIDE
The optimum dose of clarithromycin in PPI triple therapies is still debatable, as randomised studies indicate that, on the one hand, the minimum dose is different depending on the other components, and, on the other, side effects such as taste disturbances and diarrhoea are controlled mainly by the dose.

The dose of clarithromycin was the subject of a meta-analysis by Huang et al. Analysing 26 treatment arms of one week triple therapies with PPI, clarithromycin, and metronidazole, they found that 500 mg clarithromycin twice a day resulted in a significantly higher H pylori cure rate (90% intention to treat (ITT)) than 250 mg twice a day (82% ITT). The same holds true for the triple therapy with PPI, clarithromycin, and amoxycillin (91% ± 80% ITT).

A drawback of this meta-analysis is that no data were provided on the randomisation. An earlier randomised study indicated that 250 mg clarithromycin is equivalent in the combination PPI, clarithromycin, and metronidazole.

When used in combination with lansoprazole and amoxycillin, Yang et al found that 250 mg clarithromycin was satisfactory only when used for two weeks (92% per protocol (PP)), but 500 mg was still more effective (96% PP).

Clarithromycin in combination with a PPI and a nitromidazole may be replaced by azithromycin without loss of efficacy. Whereas Caselli et al achieved a 93% eradication rate using azithromycin 500 mg for three days, Seelis et al achieved only 47% with the same dose, but 93% using azithromycin 500 mg for six days.

DOSE OF ACID SUPPRESSIVE AGENT
The Maastricht Consensus Report recommends twice daily standard doses of the PPI in PPI triple therapy whereas Bazzoli et al

---

Figure 1 Helicobacter pylori eradication rates with triple therapy comprising proton pump inhibitor (RBC = ranitidine bismuth citrate), clarithromycin, and a nitroimidazole for seven days. The numbers of the references from which the data are taken are given on the x axis.
and clarithromycin, 7 v 14 days; in the USA with lansoprazole, clarithromycin, and amoxycillin, 10 v 14 days; in Spain with omeprazole, clarithromycin, and amoxycillin, 6 v 12 days for peptic ulcer disease; and in Germany with pantoprazole, clarithromycin, and metronidazole 7 v 14 days. Significantly higher H pylori cure rates with longer treatments were achieved in Croatia with omeprazole, amoxycillin, and metronidazole as well as with omeprazole, clarithromycin, and amoxycillin (7 v 14 days), in Spain with omeprazole, clarithromycin, and amoxycillin (6 v 12 days) for patients with non-ulcer gastritis, and in Taiwan with lansoprazole, clarithromycin 250 mg once daily, and amoxycillin (7 v 14 days). In the last of these studies, however, the dose of clarithromycin used was below the standard. None of these studies provided data on resistance. In contrast, reducing treatment duration to less than one week has proved to be disadvantageous. Are more agents better?

Authors presenting studies on quadruple or even quintuple therapies intended to increase the eradication rate further, to reduce the treatment time, or to establish a second line treatment after failure of H pylori eradication. No convincing data have been provided to support the notion that the use of more than three agents is superior as a first line treatment in eradicating H pylori.

The quadruple therapy of PPI, bismuth, metronidazole, and tetracycline, introduced by Hosking al, de Boer et al, and Borody et al, is highly efficacious when used as an initial treatment and when the high numbers of tablets are taken for one week. Reducing the treatment duration to four or two days has now been shown to lead to a loss of efficacy, particularly in patients harbouring a metronidazole resistant strain. A treatment introduced by Daskalopoulos et al using the five agents colloidal bismuth subcitrate, tetracycline, metronidazole, roxithromycin, and lansoprazole resulted in a higher eradication rate than with three or four of these agents, but the rate achieved did not exceed 92% PP. Moreover, the agents were given for two weeks and no data on side effects were presented.

After failure of dual therapy, the combination of omeprazole with not only two but all three standard antimicrobial agents, all given for five days, was no more efficacious (93% PP, 90% ITT) than omeprazole, clarithromycin, and metronidazole for seven days. Another two groups presented studies on newly created quadruple therapies as second line treatments. The eradication rates were satisfactory for a second line treatment: omeprazole, azithromycin, amoxycillin, and colloidal bismuth subcitrate for two weeks (81% PP, 77% ITT); omeprazole, metronidazole, amoxycillin, and bismuth citrate for two weeks (82% PP, 70% ITT). However, in both studies no data on the initial treatment or the pattern of microbial resistance after treatment failure were given. The former therapy was reported to be linked

Figure 2 Helicobacter pylori eradication rates with triple therapy comprising proton pump inhibitor (RBC = ranitidine bismuth citrate), clarithromycin, and amoxycillin for seven days. The numbers of the references from which the data are taken are given on the x axis. LAN 30, lansoprazole 15 mg twice daily; LAN 60, lansoprazole 30 mg twice daily; OME 40, omeprazole 20 mg twice daily; PAN 40, pantoprazole 40 mg once daily; PAN 80, pantoprazole 40 mg twice daily.

Figure 3 Helicobacter pylori eradication rates with triple therapy comprising proton pump inhibitor, amoxycillin, and metronidazole for seven days. The numbers of the references from which the data are taken are given on the x axis. OME 20, omeprazole 20 mg once daily; OME 40, omeprazole 40 mg once daily.

originally used a once daily standard dose. Three abstracts of large studies investigating the dose of PPI clearly support the Maastricht recommendation. In a randomised study by Buda et al, two daily doses of 30 mg lansoprazole proved to be significantly more efficacious (88% PP, 83% ITT) than 15 mg twice a day (76% PP, 71% ITT) in combination with clarithromycin and amoxycillin. Applying the same antibiotics in a randomised study, Lamouliate et al found pantoprazole 40 mg to be significantly superior when used twice a day (81% PP) compared with a once daily dosage (59%). In combination with metronidazole and amoxycillin, omeprazole 40 mg yielded a higher H pylori cure rate (74%) than omeprazole 20 mg (67%). Further evidence was provided that 400 mg ranitidine bismuth citrate is equivalent to a standard dose of PPI in triple therapy. In dual therapy with clarithromycin it may be even superior to PPI. Is longer better?

The issue of treatment duration turned out to be rather controversial in the Lisbon abstracts. Most studies confirmed that one week of treatment is sufficient in PPI triple therapy, but there may be some exceptions that are potentially due to regional differences or disease entity. No benefit from a longer treatment period was found in the following studies: in Italy with ranitidine bismuth citrate
to a side effect rate of 41%. Moreover, the question of safety of quadruple therapy was further raised by Phillips et al., reporting high blood levels of bismuth in two of eight patients after co-administration of colloidal bismuth subcitrate and omeprazole for two to four weeks, but not after bismuth subnitrate/carbonate and omeprazole.

**Is treatment efficacious and cost-effective in routine community practice?**

Two studies ascertained that *H. pylori* eradication rates are similar in the community setting to clinical trials. A cost analysis was performed by Vakil and Fennerty using a decision tree model with a follow up period of two years. The costs are dominated by cases of failed eradication, but not by the initial costs of treatment. Therefore highly efficacious treatments such as PPI based triple therapies resulted in the lowest total costs, the triple therapy with a PPI, clarithromycin, and metronidazole being the most cost-effective. Regimens with eradication rates of less than 90% are not cost-effective in routine practice.

**Is treatment efficacy dependent on disease entity?**

The GU-Mach study confirmed comparable *H. pylori* eradication rates in the treatment of gastric and duodenal ulcer. Comparing *H. pylori* eradication in peptic ulcer disease and non-ulcer dyspepsia, two studies detected lower eradication rates in the treatment of non-ulcer dyspepsia. No possible reasons are given, but lower compliance may be the cause. Georgopoulos et al. found no difference between ulcer disease and non-ulcer dyspepsia, but lymphoid follicles were a negative predictor of treatment success. Again, it was confirmed that healing of uncomplicated duodenal ulcer is achieved by an effective one week *H. pylori* treatment without consecutive acid suppression. In contrast, gastric ulcer healing may take a long time despite continued PPI therapy.

**What is the impact of microbial resistance?**

The reported prevalences of pretreatment resistance were similar to previous reports from Europe: macrolide resistance about 2–3%; nitromidazole resistance about 30%. Exceptions were metronidazole resistance in Greece of 44%, macrolide resistance in France of 10.5% or about 15%, and an increase in macrolide resistance in Portugal from 5.6% (1990–1993) to 11.2% (1994–1997) in the past seven years.

The impact of metronidazole resistance on eradication rates was confirmed. In the face of metronidazole resistance, *H. pylori* eradication rates were 75% and 74% when a triple therapy with PPI, clarithromycin, and metronidazole was used, and 62% when a four day quadruple therapy was used. In a dual antibiotic treatment without a PPI, the impact of metronidazole resistance is considerably greater. Poor eradication of less than 50% ensues when clarithromycin resistance is present. In contrast, Megraud et al. reported an *H. pylori* cure rate of 11 in 12 cases with clarithromycin resistant strains using dual therapy with clarithromycin and ranitidine bismuth citrate.

Again confirmed, although in small numbers, was the occurrence of post-treatment resistance to clarithromycin in 50% or more of cases with failure after macrolide containing regimens.

Whereas second line treatment of patients with persistent *H. pylori* infection after dual therapy with omeprazole and amoxicillin is highly efficacious with triple therapy, second line treatment after failure of triple therapy still yields inconsistent and partly unsatisfactory results. The recommended quadruple therapy with PPI, bismuth, metronidazole, and tetracycline led to eradication rates of 72%, 50%, and 93%, whereas with the modified quadruple therapies mentioned above the eradication rates were higher (81%, 82% and 86%).

Almost all of the studies on second line therapies specified neither the initial therapy nor the pattern of resistance after initial treatment failure. Obviously, the success of the second line treatment depends on the components of the initial treatment. Thus no general conclusion can be drawn from the studies presented on second line treatments. However, it has been confirmed that it is of benefit to determine the resistance status before planning the second line treatment. A small study reported a 75% eradication rate with omeprazole, amoxicillin, and ciprofloxacin in cases with double resistance against clarithromycin and metronidazole. This needs further confirmation, as previous experience with ciprofloxacin in *H. pylori* eradication therapy has been very poor.

H pylori eradication therapies

S69

12 Damman HG, Fölsch UR Hahn EG, et al. 7 vs 14 days
treatment with pantoprazole, clarithromycin, and metroni-
dazole for cure of H. pylori infection in duodenal ulcer patients

13 Frevel M, Duake H, Janisch HD, et al. Pantoprazole plus
clarithromycin and metronidazole versus pantoprazole plus
clarithromycin and amoxicillin for therapy of H. pylori

eradication rate with a one-week triple regime containing
ranitidine bismuth citrate (RBC) [abstract]. Gut 1997;47:
A99.

15 Adamek R, Pfaffenbach B, Smyianski C. Does pre-
treatment with pantoprazole affect the efficacy of a modern
triple therapy in HP cure? [abstract]. Gut 1997;47(suppl 1):A95

16 Katicic M, Presecki V, Marusic M, et al. Effectiveness in
eradicating Helicobacter pylori in gastric ulcer patients

17 Krause R, Pruit R, Lukasik N, et al. New dual-7-day
therapy for Helicobacter pylori: a multicentre comparative

18 Chen CY, Sheu MZ, Lee SC. Intravenous dual therapy
and oral new triple therapy in Helicobacter-related ulcer bleed-
ing with major sign of recent hemorrhage [abstract].
Gut 1997;47(suppl 1):A98.

19 Pieramaric O, Zanetti MW, Innerhofer M. Outcome of
omeprazole-based dual and triple therapy for Helicobacter
pylori eradication: do gastroduodenal disease and age play

20 Buda A, Dal Bo N, Kusstratscher S, et al. Comparison of two
treatment with pantoprazole, clarithromycin and metroni-
dazole in the eradication of Helicobacter pylori (Hp) infection

21 Vakil N, Fennerty B. Cost-effectiveness of H. pylori eradica-
tion regimes: efficacy vs effectiveness [abstract]. Gut 1997;
47(suppl 1):A89.

therapy with pantoprazole a

23 de Boer WA, van Eten RJXM, Schneeberger PM. Four days
lanosoprazole-quadruple therapy in the routine treatment of
Helicobacter pylori infection [abstract]. Gut 1997;47(suppl 1):
A97.

24 Ho SY, Yan XX. Does pentuple therapy offer any advantage over triple therapy or quadruple
therapy in the eradication of H. pylori [abstract]. Gut 1997;
47(suppl 1):A105.

25 de Boer WA, Driessen WMM, Janisz AR, et al. Quadruple
therapy compared with dual therapy for eradication of H.
pylori in ulcer patients: results of a randomized prospective
single-center study. Eur J Gastroenterol Hepatol 1995;7:
1189–94.

26 de Boer WA, Driessen WMM, Janisz AR, et al. Effect of acid
suppression on the efficacy of treatment for Helicobacter pylori

enhances efficacy of triple therapy in eradicating Helico-

28 Kist M, Strobel S, Folsch UR, et al. Evolution of Heli-
cobacter pylori infection [abstract]. Gut 1995;41:
A109.

29 Mégraud F, Pichavant R, Palegry D, et al. Effect of azithromy-
cin (C) for Helicobacter pylori (HP) infection. 6 vs 12 days.

30 Buda A, Dal Bo N, Kusstratscher S, et al. Pantoprazole plus
clarithromycin in the eradication of Helicobacter pylori (Hp)
therapy is more effective than omeprazole with clarithromycin

therapy for Helicobacter pylori: a multicentre comparative

32 de Boer WA, van Eten RJXM, Schneeberger PM. Four days
lanosoprazole-quadruple therapy in the routine treatment of
Helicobacter pylori infection [abstract]. Gut 1997;47(suppl 1):
A97.

33 de Boer WA, van Eten RJXM, Schneeberger PM. Four days
lanosoprazole-quadruple therapy in the routine treatment of
Helicobacter pylori infection [abstract]. Gut 1997;47(suppl 1):
A97.