The European meeting on *Helicobacter pylori*: therapeutic news from Lisbon

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**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, amoxicillin, 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 amoxicillin (91% vs 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 amoxicillin, 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 nitroimidazole 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.*...
and clarithromycin, 7 v 14 days; in the USA with lansoprazole, clarithromycin, and amox-
ycin, 10 v 14 days; in Spain with omeprazole,
clarithromycin, and amoxicillin, 6 v 12 days for
peptic ulcer disease; and in Germany with pantoprazole, clarithromycin, and metronida-
zole 7 v 14 days. Significantly higher H pylori
cure rates with longer treatments were achieved
in Croatia with omeprazole, amoxicillin, and
metronidazole as well as with omeprazole,
clarithromycin, and amoxicillin (7 v 14 days),
in Spain with omeprazole, clarithromycin, and
amoxicillin (6 v 12 days) for patients with non-ulcer gastritis, and in Taiwan with
lansoprazole, clarithromycin 250 mg once
daily, and amoxicillin (7 v 14 days). In the last
of these studies, however, the dose of clarithro-
mycin 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 tetracyclin, introduced by
Hosking et al, de Boer et al, and Borody et al,
highly efficacious when used as an initial
treatment and when the high numbers of
tables 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 metroni-
dazole resistant strain.

A treatment introduced by Daskalopoulos et al using the five agents colloidal bismuth sub-
citrate, tetracyclin, metronidazole, roxithromy-
cin, 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 combina-
tion 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
quadraple therapies as second line treatments.
The eradication rates were satisfactory for a
second line treatment: omeprazole, azithromy-
cin, amoxicillin, and colloidal bismuth subci-
strate for two weeks (81% PP, 77% ITT); omeprazole, metronidazole, amoxicillin, 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

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 treat-
ment 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
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 lansopra-
zole 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 amoxicillin. Applying the
same antibiotics in a randomised study,
Lamouliatte et al found pantoprazole 40 mg
to be significantly superior when used twice a
day (81% PP) compared with a once daily dos-
age (59%). In combination with metronidazole
and amoxicillin, omeprazole 40 mg yielded a
higher H pylori cure rate (74%) than omepra-
zole 20 mg (67%). Further evidence was pro-
vided 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.

Figure 2 Helicobacter pylori eradication rates with triple therapy comprising proton pump
inhibitor (RBC = ranitidine bismuth citrate), clarithromycin, and amoxicillin 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.

References or
to a side effect rate of 41%.\textsuperscript{40} Moreover, the question of safety of quadruple therapy was further raised by Phillips \textit{et al},\textsuperscript{42} 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 subcitrate/ carbonate and omeprazole.

Is treatment efficacious and cost-effective in routine community practice? Two studies ascertained that \textit{H pylori} eradication rates are similar\textsuperscript{43} achieved by an effective therapy with \textit{H pylori} 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\textsuperscript{8} and also the study by Katicic \textit{et al}\textsuperscript{16} confirmed comparable \textit{H pylori} eradication rates in the treatment of gastric and duodenal ulcer. Comparing \textit{H pylori} eradication in peptic ulcer disease and non-ulcer dyspepsia, two studies\textsuperscript{10} detected lower eradication rates in the treatment of non-ulcer dyspepsia. No possible reasons are given, but lower compliance may be the cause. Georgopoulos \textit{et al}\textsuperscript{19} 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 \textit{H pylori} treatment without consecutive acid suppression.\textsuperscript{9 44–49}

In contrast, gastric ulcer healing may take a long time despite continued PPI therapy.\textsuperscript{45 47}

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%; nitrimidazole resistance about 30%.\textsuperscript{4 22 30 51} Exceptions were metronidazole resistance in Greece of 44%,\textsuperscript{46} macrolide resistance in France of 10.5%\textsuperscript{21} or about 15%,\textsuperscript{29} and an increase in macrolide resistance in Portugal from 5.6% (1990–1993) to 11.2% (1994–1997) in the past seven years.\textsuperscript{51}

The impact of metronidazole resistance on eradication rates was confirmed. In the face of metronidazole resistance, \textit{H pylori} eradication rates were 75% and 74%\textsuperscript{47} when a triple therapy with PPI, clarithromycin, and metronidazole was used, and 62% when a four day quadruple therapy was used.\textsuperscript{41} In a dual antibiotic treatment without a PPI, the impact of metronidazole resistance is considerably greater.\textsuperscript{4} Poor eradication of less than 50% ensues when clarithromycin resistance is present.\textsuperscript{40} In contrast, Mégraud \textit{et al}\textsuperscript{50} reported an \textit{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\%\textsuperscript{4} or more\textsuperscript{40 52} of cases with failure after macrolide containing regimens.

Whereas second line treatment of patients with persistent \textit{H pylori} infection after dual therapy with omeprazole and amoxicillin is highly efficacious with triple therapy,\textsuperscript{5} 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%,\textsuperscript{53} 50%,\textsuperscript{52} and 93%,\textsuperscript{17} whereas with the modified quadruple therapies mentioned above the eradication rates were higher (81%,\textsuperscript{40} 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.\textsuperscript{49} 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.\textsuperscript{50 52} A small study\textsuperscript{42} 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 \textit{H pylori} eradication therapy has been very poor.

11 Spadaccini A, De Fains C, Sciampa G, et al. Lansoprazole or ranitidine bismuth citrate based triple therapies for Helico-


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