Clinical aspects in Helicobacter pylori infections

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CHAPTER 4

Helicobacter pylori eradication therapy in The Netherlands
**Helicobacter pylori eradication therapy in The Netherlands**


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**Summary**

**Background:** Helicobacter pylori (Hp)-cure rates vary in different geographical regions because of differences in hosts as well as in H. pylori strains.

**Objective:** To systematically review all available data in the literature to determine Hp-eradication rates in The Netherlands.

**Methods:** A search of all published trials on Hp eradication therapy, performed in The Netherlands was performed via electronic database search, handsearching of abstracts from scientific meetings and checking reference lists of pharmaceutical companies. Full papers and abstracts were included. Data on anti-Hp therapies were pooled based on duration and combination of drugs. Only triple- and quadruple eradication regimens were studied. Dual therapies were excluded except for ranitidine bismuth citrate based dual therapies.

**Results:** We analyzed 38 study arms, involving 2197 patients. Twenty different pooled regimens were studied with a mean ITT eradication rate of 83% (range 35-96%).

There were no significant differences in the percentage of patients that stopped treatment due to adverse events between the groups. In these pooled regimens only bismuth combined with tetracycline and metronidazole for 1 or 2 weeks showed a significantly lower efficacy in metronidazole resistant strains compared to metronidazole sensitive strains. The prevalence of metronidazole resistant strains in The Netherlands showed large regional differences (7-50%).

**Conclusions:** A therapy should be tested in a defined population before becoming standard reference. Several eradication regimens studied in The Netherlands yield acceptable cure rates of 80% or more on an intention to treat basis. We advise to take the local prevalence of metronidazole resistance into account when choosing a first choice eradication regimen.

**Introduction**

Indications for the eradication of Helicobacter pylori ( Hp) have broadened over the last years. The Maastricht consensus advises eradication therapy in all H. pylori positive patients with peptic ulcer disease, in patients with low grade gastric mucosa associated lymphoid tissue (MALT) lymphoma, in patients with gastritis with severe macro- or microscopic abnormalities, and in
Helicobacter pylori positive patients with functional dyspepsia in whom no other causes of symptoms can be identified. \(^1\)

Because \(H.\) \(pylori\) cure rates can vary in different geographical regions, several authors suggest that the results of possibly successful eradication regimens should be confirmed in a certain geographical area before their use can be promoted in that area.\(^2,3\)

To help the clinician in choosing an optimal therapy to cure \(H.\) \(pylori\) infection, we systematically reviewed all published anti-\(H.\) \(pylori\) therapy trials performed in The Netherlands.

**Methods**

*Locating and selecting studies.*

A search of all published trials on \(H.\) \(pylori\) eradication therapy, performed in The Netherlands was performed via a MEDLINE and EMBASE electronic database search from 1983 to May 1998 and via handsearching of abstracts from scientific meetings plus checking reference lists of pharmaceutical companies.

The inclusion criteria of trials for this review were:

1. Published \(H.\) \(pylori\) eradication therapy trials, prospective and/or retrospective, published as abstract or full paper.
2. Eradication therapy consisting of triple- or quadruple therapies. Mono- and dual therapy trials were not included, except for dual therapy trials with ranitidine bismuth citrate.
3. An intention-to-treat (ITT) and/or per-protocol (PP) eradication percentage was required or figures should be given so that ITT and/or PP eradication percentage could be calculated per treatment arm.

Publications identified as duplicates were excluded.

**Collecting data**

Each study arm was assigned a unique study number. Two different reviewers independently analyzed each study arm and data were recorded on a form. Both forms were compared and errors and disagreements were discussed and corrected. The final data were entered in an ACCESS database. This database has multiple automatic error control functions and was manually checked for errors by another investigator.

Different eradication regimens were pooled into 0, 1 and 2 week regimens, based on the duration and combination of the drugs, regardless of dosage and dosing intervals (Table I, next page). One-week therapy is defined as the regimen as a whole was given between 4 to 9 days. Two-week therapy was defined as the regimen was given for more than 9 days. When a therapy was given for less than 4 days it was defined as a 0-week therapy.

Intention to treat analysis (ITT) includes all \(H.\) \(pylori\) positive patients that were randomized or started with therapy. All patients who had no follow up are considered not eradicated ('worst-case' scenario). We defined the per protocol (PP) analysis as all treated patients who complied
Table 1 Treatment groups

<table>
<thead>
<tr>
<th>Therapy-code</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAM1</td>
<td>Bismuth/amoxicillin/metronidazole 1 week</td>
</tr>
<tr>
<td>BAM2</td>
<td>Bismuth/amoxicillin/metronidazole 2 weeks</td>
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<tr>
<td>BCT2</td>
<td>Bismuth/clarithromycin/tetracyclin 2 weeks</td>
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<td>BTM2</td>
<td>Bismuth/tetracycline/metronidazole 2 weeks</td>
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<td>Omeprazole/amoxicillin/clarithromycin 1 week</td>
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<td>OBA2</td>
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<td>Lansoprazole/bismuth/tetracycline/metronidazole 0 week</td>
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<td>Lansoprazole/bismuth/tetracycline/metronidazole 1 week</td>
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<td>Omeprazole/bismuth/tetracycline/metronidazole 1 week</td>
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<tr>
<td>RAC</td>
<td>Ranitidine bismuth citrate/amoxicillin/clarithromycin 1 week</td>
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<td>Ranitidine bismuth citrate/clarithromycin 2 weeks</td>
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<tr>
<td>RTM2</td>
<td>Ranitidine bismuth citrate/tetracyclin/metronidazole 2 weeks</td>
</tr>
</tbody>
</table>


0w = '0-week therapy' i.e. therapy duration of less than 4 days.
1w = '1-week therapy' i.e. therapy duration between 4 to 9 days.
2w = '2-week therapy' i.e. therapy duration of more than 9 days.

to the study protocol, had complete follow up and took at least 70% of the prescribed medication. If possible, eradication percentages were recounted to this definition. In subgroups the intention to treat analysis was used.

Analysis of the data

The statistical computer program SPSS was used to analyze and summarize the data. Per pooled therapy group a weighed eradication rate was calculated according to intention to treat analysis and per protocol analysis. An equal effect model was used to calculate these eradication rates with their 95% confidence intervals. The difference in eradication rates was considered statistically significant if the 95% confidence interval of this difference did not embrace the value zero.

Results

A total of 30 papers, involving 38 study arms and 2197 patients fulfilled the inclusion and exclusion criteria and were analyzed. Twelve first authors published all studies, and three different groups in the Netherlands published over 80% of all studied patients.
Twenty-six study arms were published as full papers and 12 as abstracts only. Twenty study arms were part of a randomized trial. Two study arms were from double-blind studies, 2 from single blind studies; the rest were open label studies.

**Bismuth based triple therapy.**

The bismuth based triple therapies have been studied in 13 study arms, involving over 704 patients in the Netherlands.\(^4\)\(^{-13}\) The ITT eradication rate in this group was below 80%, except for bismuth-tetracycline-metronidazole for 2 weeks (BTM2) which shows exceptionally good ITT and PP eradication rates of 94 and 96% respectively, with narrow 95% confidence intervals (Table 2). Bismuth combined with amoxycillin and metronidazole for 1 week (BAM1) was given in one study published in 1994\(^4\), with an ITT eradication rate of only 35%. Since 73% of these patients harbored a metronidazole resistant strain, this must have been a selective patient group. Probably most patients in this group were former treatment failures to bismuth-metronidazole dual therapy.

Bismuth and metronidazole combined with tetracycline (BTM) yield superior cure rates compared to the combination with amoxycillin (BAM). Patients with metronidazole resistant

<table>
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<th>Therapy code</th>
<th>Number of study arms</th>
<th>ITT N/n</th>
<th>Eradication %</th>
<th>95% CI</th>
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<td>70-86</td>
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<td>75-94</td>
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<td>1</td>
<td>26/36</td>
<td>72</td>
<td>57-88</td>
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<td>72</td>
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<td>78</td>
<td>73-84</td>
<td>157/190</td>
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<td>86</td>
<td>77-95</td>
<td>50/56</td>
<td>89</td>
<td>81-98</td>
</tr>
</tbody>
</table>

\(N = \) number of eradicated patients * \(n = \) total number of patients * 95% CI = 95% confidence interval
strains, treated with bismuth-tetracycline-metronidazole for 1 or 2 weeks, show significantly lower cure rates than patients with metronidazole sensitive strains, with a mean drop in efficacy of 97 to 44% (Table 3).

PPI triple therapy

PPI triple therapies have been investigated in the Netherlands in 8 study arms, involving 501 patients. The reported eradication rates in Dutch studies seem to be somewhat lower than reported elsewhere with a mean ITT cure rate of 84% for the one-week PPI triple therapies. All one-week PPI triple therapies were given for 7 days, all two-week therapies for 14 days. Omeprazole combined with clarithromycin and metronidazole for two weeks (OCM2) had the highest cure rate of 96%.

The low cure rates for omeprazole combined with amoxycillin and metronidazole for 2 weeks (OAM2) may be caused by the fact that these patients were former treatment failures to omeprazole-amoxycillin dual therapy (Table 2).

There is a trend that metronidazole resistant strains show lower mean eradication rates, however the 95% confidence intervals overlap in all PPI-triple therapy groups.
**Quadruple therapy**

Quadruple therapy has been investigated frequently in the Netherlands, mostly by De Boer in the south of the Netherlands. A total of 11 study arms involving 602 Dutch patients were published using quadruple therapy (Table 2). In three study arms quadruple therapy was given for one or two days only (LBTM0), all with eradication rates below 60%. In four studies (3 LBTM1 and 1 OBTM1) quadruple therapy was given for 4 days with a mean ITT and PP eradication rate of 89 and 91% respectively. All other quadruple therapies were given for 7 days, with ITT and PP eradication rates of 93 and 95%, respectively. No Dutch published studies with two-week quadruple studies were found. Omeprazole-bismuth-tetracycline-metronidazole for one week (OBTM1) showed the highest mean ITT eradication rate in this group of 93%.

In patients with metronidazole resistant strains the mean efficacy of quadruple therapy is less than in patients with metronidazole sensitive strains, however since the 95% confidence intervals still overlap, this difference is not significant (Table 3).

**Ranitidine bismuth citrate combination therapy**

Ranitidine bismuth citrate combinations have been investigated in the Netherlands in 6 different study arms involving 390 patients with a mean ITT and PP eradication rate of 92% and 95% respectively (Table 2). Ranitidine bismuth citrate in combination with clarithromycin and metronidazole for 1 week (RCM1) showed the highest cure rate of 96% on an intention to treat basis.

No differences in efficacy were found between patients with metronidazole resistant or sensitive strains.
The prevalence of metronidazole resistant strains within the study population or within that specific region as reported in the studies was also collected and is called the 'background metronidazole resistance' (Table 3).

As shown in Figure 1, the reported prevalence of metronidazole resistant strains shows large regional differences with almost 50% in the Amsterdam region and about 10% in other parts of the Netherlands.

Side effects were generally minor and the reported number of patients who stopped therapy because of side effects was below 1% in all pooled therapy groups. Patients with former failure of eradication treatment were studied in one trial, where 20 patients were treated with omeprazole-amoxicillin-metronidazole for 2 weeks (OAM2) after failure of omeprazole-amoxicillin dual therapy. Detailed information on prior therapy failure was not mentioned in other studies.

In the studies performed in the Netherlands mostly both ulcer and functional dyspepsia patients were enrolled. The two pantoprazole based triple therapies included only functional dyspepsia patients. In four other studies only ulcer patients were enrolled (1 BAM2, 1 BTM1, 1 OBTM, and 1 PC2).

Discussion

The different H. pylori eradication therapies have become increasingly effective in eradicating the Helicobacter pylori, however in 10-30% of cases currently advised therapies still fail to eradicate the Helicobacter pylori. Factors that may cause eradication failure are for example the choice of the eradication regimen, non-compliance, antibiotic resistance, former therapy failure and the indication for eradication therapy, i.e. H. pylori eradication rates are higher in ulcer patients than in patients with functional dyspepsia. Probably also other underlying conditions can lead to eradication failure.

H. pylori appears to be a highly heterogeneous microorganism and data suggest that a specific genotype may exist within a particular geographic area or within a particular ethnic group. Differences among bacterial strains may induce divergent clinical or pathological effects, and strain differences may also alter the efficacy of eradication regimens. Also differences within the host can cause eradication failure. Therefore, several authors state that the results of possibly successful eradication regimens should be confirmed in a certain geographical area before their use can be promoted in that area.

In the Netherlands bismuth based triple therapies, PPI-triple therapies, quadruple therapies as well as ranitidine bismuth citrate based therapies have been investigated (Table 2). We have not looked at dual therapy, except for ranitidine bismuth citrate based dual therapies since we feel these therapies yield unacceptable low eradication rates.

When looking at the differences in eradication rates between patients with metronidazole sensitive and resistant strains, there is a trend that metronidazole resistant strains show lower mean eradication rates, however this is only significant for bismuth-tetracycline-metronidazole...
Helicobacter pylori eradication therapy in the Netherlands

combination therapy for 1 or 2 weeks. In all the other therapy groups the 95% CI of the cure rates overlap between patients harboring metronidazole resistant or sensitive strains (Table 3). Clarithromycin resistance is generally regarded as a factor leading to eradication failure with clarithromycin containing regimens. Clarithromycin resistance of H. pylori is very rare in the Netherlands: only 7 patients have been described in trial settings. Two patients were treated with pantoprazole-amoxicillin-clarithromycin for 1 week (PAC1) and one with ranitidine bismuth citrate-clarithromycin for 2 weeks (RC2), these were all failures of therapy. Van der Wouden et al described four patients with a clarithromycin resistant strain that were treated with ranitidine bismuth citrate-clarithromycin-metronidazole for 1 week (RCM1) who were all eradicated.31

The data presented are a non-randomized comparison. Patient-characteristics, drug compliance, the prevalence of antimicrobial resistance and other prognostic factor may differ between the populations. Several of the studies have only been published as abstract and not (yet) as full paper in a peer reviewed journal. The different studies have different design and study mixed patient material. Since the total number of patients in all groups remains relatively low, the 95% confidence intervals of the eradication rates often overlap. Therefore we cannot advise a single regimen based on the data presented here.

The aims of therapy should be to prescribe a simple, well tolerated regimen, which is easy to comply with, is cost effective and achieves an eradication rate of over 80% on an intention to treat basis. Several regimens included in this review comply with those requirements. Between the effective regimens, patient acceptance and the local prevalence of antimicrobial resistance should guide the clinician in selecting a therapeutic regimen.
References


17. Tan AC, den Hartog G, Meijer JW, Thies JE, de Vries RA, Mulder CJ. No additional value of bis-


29. Van der Wouden EJ, Thijs JC, Van Zwet AA, Kooy A, Kleibeuker JH. One week triple therapy with ranitidine bismuth citrate (RBC), clarithromycin (CLA) and metronidazole (MET) vs two week dual therapy with RBC and CLA for H. pylori (Hp) infection: results of a randomized controlled trial. Abstract Springmeeting Netherlands Society of Gastroenterology 1998.


38. van Doorn LJ, Quint W, Schneeberger P, Tytgat GM, de Boer WA. The only good *Helicobacter pylori* is a dead *Helicobacter pylori* [letter; comment]. Lancet 1997;350(9070):71-2.