Clinical aspects in Helicobacter pylori infections

Houben, M.H.M.G.

Citation for published version (APA):
CHAPTER 7

PPI triple therapy failure in *Helicobacter pylori* infections:
retreatment with PPI triple therapy or quadruple therapy?
PPI-triple therapy failure in *Helicobacter pylori* infection: re-treatment with PPI-triple therapy or quadruple therapy?

M.H.M.G. HOUBEN*, P.R. TUINMAN†, D. VAN DE BEEK‡, B.W.M. VAN ’T HOFF‡, A. VAN DER ENDE†, F.J.W. TEN KATE*, G.N.J. TYTGAT‡.

Department of Gastroenterology*, Medical Microbiology† and Pathology*, Academic Medical Center, Amsterdam, The Netherlands.

Submitted

**Summary**

**Background.** Proton pump inhibitor (PPI)-based triple therapies have consistently achieved eradication rates above 80% and are widely employed as first-line treatments for *Helicobacter pylori* infections. Second-line therapy in patients who failed a first-line PPI-triple therapy is problematic. The aim of this study was to compare the efficacy of a second-line PPI-triple versus quadruple therapy, in patients with primary PPI-triple therapy failure.

**Materials and methods.** Patients who failed a PPI-triple therapy were randomly allocated to second-line therapy with PPI-triple therapy consisting of omeprazol 20 mg bid, clarithromycin 500 mg bid and metronidazole 500 mg bid (OCM), or quadruple therapy consisting of omeprazol 20mg bid, bismuth subcitrate 120 mg qid, tetracycline 500mg qid and metronidazole 500mg tid (OBTM), both for 7 days. All failures of the second-line OCM treatment were offered a third-line OBTM regimen. Cure of *H. pylori*-infection was defined as absence of *H. pylori* in culture and histology in all biopsies, at least four weeks after completion of therapy. Antibiotic resistance was determined by E-test.

**Results.** Twenty-three patients were included. One patient, randomized to OBTM was lost to follow-up. Compliance was excellent. Eradication rates were 22% &quot; for OCM and 85% 11/13 for OBTM. The difference in cure rate between OCM and OBTM was 62% (95% CI: 29-96), p=0.0003). Resistance to clarithromycin was seen in 30% of the patients before the first-line therapy, in 48% before the second-line therapy and in 67% before the third-line therapy. Resistance to metronidazole was seen in 50% of the patients before the first-line therapy, in 55% before the second-line therapy, and in 89% before the third-line therapy. Failures of both second-line regimens were seen primarily in patients harboring resistant strains.

**Discussion.** In failures of PPI-triple therapy, second-line treatment with one week OBTM is superior to one week OCM, especially in metronidazole resistant patients. We recommend quadruple therapy in the case of PPI-triple therapy failure.
Introduction

The efficacy of proton pump inhibitor (PPI)-based triple therapy in eradicating Helicobacter pylori has been well documented. When efficacy, compliance, safety, cost-effectiveness, and simplicity of a regimen are taken into account, PPI-triple therapies are the most frequently recommended treatments world-wide. However, in 10-20% of cases, these PPI-triple therapies fail to eradicate H. pylori. The reasons for failure of PPI-triple therapies are often not known. Patient compliance and antimicrobial resistance are thought to be the major determinants of treatment failure. It is unclear what the optimal therapy is to eradicate H. pylori after PPI-triple therapy has failed. The Maastricht Consensus advised quadruple therapy in the case of PPI-triple therapy failure; however, few data exist on the efficacy of a quadruple therapy as a second-line regimen. The majority of data on the efficacy of currently used eradication regimens is based on patient populations presenting for an initial eradication attempt. Extrapolation of these findings to patients who have already experienced a failed eradication therapy is likely to be misleading. We prospectively compared the efficacy of a second-line PPI-triple versus quadruple therapy, in relation to metronidazole and clarithromycin resistance, in patients with primary PPI-triple therapy failure.

Methods

Patients between 18 and 80 years of age, who were referred to our endoscopy unit for diagnostic upper gastrointestinal endoscopy because of dyspeptic complaints, were eligible for the study. Patients had to be H. pylori-positive, as proven by positive Histopathology and/or culture of gastric biopsies, and patients had to have failed a prior PPI-triple therapy. Exclusion criteria were: previous gastric surgery, complicated ulcer, allergy to the study medication, reflux esophagitis requiring ongoing use of a proton pump inhibitor, expected non-compliance, pregnancy or breastfeeding, and severe concurrent disease. After proven failure of a prior PPI-triple therapy, patients were invited to participate in this study. All patients gave informed consent. The patients were randomly allocated to one of the following second-line regimens for 7 days each: PPI-triple therapy, consisting of omeprazole 20 mg bid, clarithromycin 500 mg bid and metronidazole 500 mg bid(OCM), or quadruple therapy, consisting of omeprazole 20mg bid, bismuth subcitrate 120 mg qid, tetracycline 500mg qid, metronidazole 500mg tid (OBTM). All failures of the second-line OCM treatment were offered a third-line OBTM regimen. The patients were questioned about compliance and side effects. Patients who were judged to be in need of further treatment after the antimicrobial therapy were prescribed antacids or H2-receptor antagonists. No proton pump inhibitors, antibiotics or bismuth-compounds were allowed during follow-up.
**Assessment of H. pylori status and susceptibility testing**

Upper endoscopy was performed at baseline and four to six weeks after completion of the treatment courses. At each endoscopy at least six biopsies were taken: two for histology and one for culture, from both antrum and corpus. Cure of *H. pylori*-infection was defined as absence of *H. pylori* in culture and histology in all biopsies.

**Microbiological analysis**

At each endoscopy, one antrum and one corpus biopsy were taken for culture. The biopsy specimens were inoculated on fresh Columbia agar plates containing 7% horse blood and cultured in microaerophilic conditions at 37 °C. After 3 days the grown *H. pylori* were collected using a cotton swab and suspended in 2 ml of DMEM cell culture medium. From this suspension 100 ml, containing 107-108 cfu/ml, was flooded on Colombia agar plates containing 7% horse blood. All plates were incubated at 37 °C under microaerophilic conditions for 3 and 5 days. The *H. pylori* strains were tested for metronidazole and clarithromycin susceptibility using the E-test (AB Biodisk, Sweden). The minimal inhibitory concentration (MIC) was defined as the concentration on the E-test strip closest to the point of intersection with growth on the plate. *H. pylori* was considered to be susceptible to metronidazole if the bacteria had a MIC < 4 μg/ml.12 *H. pylori* strains were regarded to be resistant to metronidazole if the bacteria had a MIC > 8 μg/ml. Patients with a MIC for metronidazole between 4 and 8 μg/ml were not included in this study. The *H. pylori* strains were considered to be resistant to clarithromycin if the bacteria had a MIC > 1 μg/ml.

**Histopathology**

Biopsies taken for histopathological assessment were placed in separate tubes containing 10% buffered formalin. Specimens were processed using the paraffin embedding technique, sectioned at four mm perpendicular to mucosal surface and stained with the Giemsa method. Complementary staining, e.g. immunohistochemical staining or in situ hybridization, was performed if necessary. The biopsies were histologically graded according to the updated Sydney system.13

**Results**

From April 1996 to January 1999, a total of twenty-three patients were recruited into the study. One patient with functional dyspepsia, who was randomized to second-line OBT M therapy, was symptom free after second-line quadruple therapy and refused follow-up endoscopy. All other patients completed the protocol. Demographic and clinical characteristics of the patients who completed the protocol are listed in **Table 1**. There were no significant differences between the two patient-groups regarding sex, age, underlying disease, type of first-line eradication regimen, or antimicrobial resistance. The patients tolerated the medication well. Five out of 13 patients in the OBT M group and four of the nine patients from the OCM group reported no side effects.
Table 1  Patient characteristics

<table>
<thead>
<tr>
<th>Second-line therapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCM</td>
<td>OBTM</td>
</tr>
<tr>
<td>Number of patients</td>
<td>9</td>
</tr>
<tr>
<td>Sex Male/Female</td>
<td>4/5</td>
</tr>
<tr>
<td>Age Mean</td>
<td>45</td>
</tr>
<tr>
<td>Range</td>
<td>24-70</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>duodenal ulcer</td>
<td>1</td>
</tr>
<tr>
<td>gastric ulcer</td>
<td>1</td>
</tr>
<tr>
<td>non ulcer dyspepsia</td>
<td>7</td>
</tr>
<tr>
<td>Failed first-line eradication regimen</td>
<td></td>
</tr>
<tr>
<td>PPI-amoxicillin-metronidazole</td>
<td>0</td>
</tr>
<tr>
<td>PPI-amoxicillin-clarithromycin</td>
<td>4</td>
</tr>
<tr>
<td>PPI-metronidazole-clarithromycin</td>
<td>5</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>resistant</td>
</tr>
<tr>
<td>sensitive</td>
<td>4</td>
</tr>
<tr>
<td>unknown</td>
<td>0</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>resistant</td>
</tr>
<tr>
<td>sensitive</td>
<td>6</td>
</tr>
<tr>
<td>unknown</td>
<td>0</td>
</tr>
</tbody>
</table>

OCM = omeprazole 20 mg bid, clarithromycin 500 mg bid and metronidazole 500 mg bid for 7 days.
OBTM = omeprazole 20mg bid, bismuth subcitrate 120 mg qid, tetracycline 500mg qid and metronidazole 500mg tid for 7 days.
NS = not significant  PPI = proton pump inhibitor

Table 2  Eradication rates

<table>
<thead>
<tr>
<th>Total</th>
<th>MS-CS</th>
<th>MR-CS</th>
<th>MS-CR</th>
<th>MR-CR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N/n</td>
<td>%</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>OCM</td>
<td>2/9</td>
<td>22</td>
<td>2.8-60</td>
<td></td>
</tr>
<tr>
<td>OBTM</td>
<td>11/13</td>
<td>85</td>
<td>55-98</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N/n</th>
<th>%</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OCM</td>
<td>2/9</td>
<td>2.8-60</td>
<td>2/4</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>OBTM</td>
<td>11/13</td>
<td>55-98</td>
<td>3/3</td>
<td>100</td>
</tr>
</tbody>
</table>

N=number of eradicated patients  n=number of treated patients  %=eradication rate  95% CI=95 percent confidence interval.
OCM = omeprazole 20 mg bid, clarithromycin 500 mg bid and metronidazole 500 mg bid for 7 days.
OBTM = omeprazole 20mg bid, bismuth subcitrate 120 mg qid, tetracycline 500mg qid and metronidazole 500mg tid for 7 days.
MS = metronidazole susceptible strains.
MR = metronidazole resistant strains.
CS = clarithromycin susceptible strains.
CR = clarithromycin resistant strains.
The difference in the overall eradication rate between OCM and OBTM is 62%. (95% confidence interval: 29-96%  
 p= 0.0003 (exact p value)).
Figure 1 Flow chart of all treated patients

22 dyspeptic patients who failed PPI triple therapy

**OBTM**

n=13

11 (85%) eradicated

2 (15%) not eradicated

1 RBC-TMI

1 not eradicated

**OBTM**

n=9

2 (22%) not eradicated

7 (78%) not eradicated

1 refused further treatment

7 OBTM retreatment

5 (71%) eradicated

2 (29%) not eradicated

**OBTM**

1 not eradicated

**OCM**

1 not eradicated

1 RBC-CM2 retreatment

1 not eradicated

**RBC-CM2**

1 not eradicated

**RBC-TMI**

1 not eradicated

Only one patient in the OBTM group had severe side effects and was unable to continue normal daily activities. All patients reported to have taken all tablets for the second-line regimen, except for one patient in the OCM group, for whom compliance is unknown.

Eradication rates are listed in Table 2. The cure rate for second-line treatment with OCM was 22% (95% CI: 2.8–60%) and for second-line OBTM treatment, the cure rate was 85% (95% CI: 55–98%). The difference in overall eradication rate between the second-line OCM and OBTM therapies is 62% (95% confidence interval: 29–96%; with a p-value according to the Fisher's exact test of 0.0003).

All patients who failed the second-line regimen were offered further treatment as is depicted in Figure 1. Five out of the seven patients (71%) who failed the second-line OCM were eradicated after a third-line OBTM regimen.

Antimicrobial susceptibility was assessed for all patients in all instances, except for two patients where no biopsies for culture were obtained before the first PPI-triple therapy. Resistance to clarithromycin was seen in six out of 20 patients (30%) before the first-line therapy, in 11 out of 23 patients (48%) before the second-line therapy and in six out of nine patients (67%) before
the third-line therapy. Resistance to metronidazole was seen in 10 of 20 patients (50%) before the first-line therapy, in 12 of 22 patients (55%) before the second-line therapy and in eight of nine patients (89%) before the third-line therapy.

**Discussion**

This randomized study shows that after failure of a PPI-triple regimen, patients still have a good chance of eradication with quadruple therapy. Even when the one patient who was lost to follow-up is included and considered a treatment failure, there is still a clearly significant difference in efficacy in favor of second-line quadruple therapy, with a p-value of 0.001. Second-line OCM is significantly less effective. Third-line quadruple therapy for one week, after failure of two sequential PPI-triple therapies, still yielded a 71% eradication rate. This study also shows that antimicrobial resistance for metronidazole and clarithromycin clearly increases after failure of a PPI-triple therapy.

Our data confirm the findings of Moshkowitz et al who found that the number of previous treatments significantly decreases the efficacy of retreatment.\(^\text{11}\) Compliance is often reported to be a major determinant in therapy failure. We questioned all our patients about compliance and side effects. Compliance was reported to be excellent in both groups, although we cannot rule out the possibility that compliance was overestimated. Side effects were more frequent in the OBTM group; however, they did not lead to discontinuation of therapy. Antimicrobial resistance is also considered a major factor in treatment failure. Recent reviews have established a negative effect of metronidazole and clarithromycin resistance on all types of PPI-triple therapy.\(^\text{14,15}\) For quadruple data are still relatively scarce and pooled analysis could not establish without doubt a significant drop in efficacy in the case of antimicrobial resistance with these therapies.

Primary antimicrobial resistance was high in our population: 30% for clarithromycin and 50% for metronidazole. Development of secondary resistance, after the first-line PPI-triple therapy, for clarithromycin was 29%; and for metronidazole, 40%. There was no selection of treatment on the basis of the antibiogram in our population. Failures of both the second-line regimens were seen mostly in patients harboring resistant strains. Therefore, the high rate of antimicrobial resistance contributes to the observed treatment failures.

Other factors that may have lead to treatment failure remain unclear. However, treatment factors (e.g. pretreatment with a PPI, dosage, dosing-interval, duration, formulation, or combination of drugs) and factors related to the host (smoking, alcohol intake, age, sex) or to differences in *H. pylori* strains can all influence eradication rates.\(^\text{8,16-20}\) These ‘other’ factors that are currently not well understood can explain why some *H. pylori* seem ‘ineradicable’ or why certain patients, who appear compliant and show no antimicrobial resistance to any of the antibiotics used, still fail sequential anti-*H. pylori* therapies.

Data in the literature on the efficacy of treatment strategies when PPI-triple therapy fails are scarce. We were able to identify four full papers and nine abstracts in which patients with PPI-
triple therapy failure were retreated with a second-line PPI-triple therapy.\textsuperscript{11,21-32} A total of 333 patients were studied in these papers, with a mean of 20 (range 7-74) patients per study arm. The mean cure rate of second-line PPI therapy in these studies was 60%, ranging from 14-100%, with a standard deviation of 24%. Lee et al showed a 33% cure rate with a repeat one-week PPI-triple therapy.\textsuperscript{31} However, an eradication rate of 80% on a per-protocol basis was seen when this PPI-triple therapy was prolonged to two weeks.\textsuperscript{31}

Data on the efficacy of second-line quadruple therapy after PPI-triple therapy failure are also conflicting, with, to our knowledge, 16 published abstracts only and one full paper.\textsuperscript{26,31-43,26,44} A total of 460 patients were studied in these papers, with a mean of 22 (range 3-69) patients per study arm. The mean cure rate of second-line quadruple therapy in these studies was 65%, ranging from 5 to 100%, with a standard deviation of 24%.

It is not clear why the data in the literature are so conflicting. Perhaps these conflicts can be explained by differences among the regimens and by the fact that in some studies different antibiotics were chosen for the second-line therapy, or the second-line therapy was selected on the basis of the antibiogram while in other studies it was not.

Recently Rinaldi et al reported second-line treatment with ranitidine bismuth citrate-tetracycl-tinidazole combination therapy for two weeks after failure of a PPI-amoxicillin-clarithromycin therapy of seven days. In that study, cure rates for the second-line therapy were reported of 82% (31 out of 38 patients) on an intention-to-treat basis and 86% (31 out of 36 patients) on a per-protocol basis.\textsuperscript{45}

In conclusion, the data on treatment failure of \textit{H. pylori} are scarce. Choosing the best available first-line treatment will prevent the development of secondary resistance, will lead to the lowest number of treatment failures, and is the most cost-effective approach. Obviously, antimicrobial resistance is important in therapy failure; however, this is not always available. When choosing quadruple therapy, the impact of antimicrobial resistance is limited. Otherwise, it seems logical to use full doses and to choose different treatment regimens to avoid the antibiotics that were previously used.

If initial eradication therapy fails and there is a clear indication to treat the \textit{H. pylori}-infection another attempt should follow and, if necessary, a third and fourth until the infection is cured. In patients who fail a first-line PPI-triple therapy, retreatment with another one-week PPI-triple therapy cannot be recommended. Whether prolonging the duration of second-line PPI-triple therapy or switching to ranitidine bismuth citrate-based triple therapy will increase the cure rates awaits further trials. For the time being, we recommend quadruple therapy in case of PPI-triple therapy failure.
References


