Eradication therapy should be different for dyspeptic patients than for ulcer patients

Wink A de Boer MD

Physicians should try to achieve an optimal cure rate with their initial Helicobacter pylori eradication therapy. Most physicians use the same treatment in all their patients. H pylori infection in patients with peptic ulcer disease (PUD) is more likely to be cured than that in patients with functional dyspepsia (FD). Differences in cure rates of 5% to 15% are usually reported, which is considered to be clinically relevant. A plausible biological explanation for this finding suggests that different strains (viralent [cagA+, vacA type s1] compared with nonvirulent strains [cagA−, vacA type s2]) in PUD and FD induce different changes in the gastric mucosa, and this facilitates or impairs antimicrobial efficacy. Physicians should be aware that most published treatment studies have included only PUD patients. This means that in clinical practice cure rates obtained in patients with FD or perhaps uninvestigated dyspepsia are usually lower than those reported in the literature. This has implications for the choice of treatment. Physicians should consider prolonging the duration of initial Helicobacter eradication therapy from seven to 10 to 14 days in patients without ulcers.

Key Words: Eradication therapy; Functional dyspepsia; Helicobacter pylori; Peptic ulcer disease

Over the past few years many physicians have adopted the strategy of treating all their patients with the same empirical treatment. This is also endorsed by some international guidelines. The choice of drugs is usually dictated by costs and the background rate of antimicrobial resistance and may, therefore, vary around the world. The optimal dosing of the selected drugs is based on the results of clinical trials. Improvement of this ‘one therapy for all’ strategy is possible if bacterial sensitivities are used to select the regimen. This is only possible after endoscopy, with culture of the biopsies obtained. Most therapies, however, are prescribed in the setting of primary health care in uninvestigated dyspepsia after a positive noninvasive diagnostic test. One therefore wonders whether a physician can improve the clinical outcome in these patients by adapting the therapeutic strategy according to the presence or absence of certain clinical characteristics.

HISTORICAL OBSERVATIONS

Quadruple therapy with proton pump inhibitors (PPIs), bismuth, tetracycline and metronidazole has been studied since 1990. In 1994, Zuckerman et al. demonstrated the eradication of H pylori in 60% of patients on quadruple therapy and the eradication rates increased to 82% on quadruple therapy with bismuth. The bismuth-containing quadruple therapy became the optimal standard therapy for H pylori eradication. However, in selected patient populations, such as those with a severely impaired gastric acid secretion, the success rate of eradication therapy was limited, with cure rates of 50-80% depending on the treatment regimen used. The cure rates of bismuth-containing quadruple therapy were lower in patients with low acid production, elderly patients, and those with a history of previous PPI use. A probiotic mixture containing the strains of Helicobacter mustelae, H influenzae, and H parainfluenzae was shown to have a beneficial effect on the elimination of H pylori in some studies, but it did not improve the cure rate in patients with low acid production. The eradication of H pylori was shown to be highly effective in patients with nonulcer dyspepsia, with cure rates of 80% compared to 60% in ulcer patients. Therefore, it is important to consider the characteristics of the patients before initiating eradication therapy.
1991. This regimen, prescribed for seven days, has been found to be extremely effective, with a cure rate of nearly 100%, even in the presence of metronidazole resistance (9). This provoked studies exploring shorter treatment durations. In the Netherlands, four-day quadruple therapy was found to perform well (rate of cure greater than 90%) in metronidazole-sensitive strains, but less so in metronidazole-resistant strains (10-14). Studies showed that with quadruple therapy, most cures occur in one to four days. In these studies, a high redundancy with seven-day quadruple therapy was demonstrated. The regimen is less vulnerable to noncompliance when compared with PPI triple therapy, where short treatment duration leads to loss in efficacy.

One-day and two-day quadruple therapies have been explored (15-18), but these extremely short regimens proved to be ineffective, with a cure rate of only 60% to 76%. Metronidazole resistance was an important determinant for failure. It was clear that in the subgroup of patients with sensitive *H. pylori* strains, other factors determined why some treatments failed and others were effective. Patient compliance was excellent with these very short treatments and could not explain the failures. It was found that smokers did worse than nonsmokers, and patients with ulcers did better than those with functional dyspepsia (FD). Van der Hulst et al (19) had also shown a higher cure rate in peptic ulcer disease (PUD) patients (60 of 76, 79%) than that in patients with FD (46 of 79, 58%). They (19) also found that the cure rate was higher in patients infected with a *cagA*-positive *H. pylori* strain (73% versus 52%) than patients with a *cagA*-negative strain (19). Vandoorn et al (20) analyzed the strains in patients we had included for a one-day quadruple treatment study. *CagA* positivity was strongly associated with the type s1 *vacA* allele (P=0.007). Patients with peptic ulcers were more frequently positive for *cagA* and the *vacA* s1 allele than patients with FD (P=0.146 and P=0.012, respectively). A higher cure rate was found for the more pathogenic *vacA* type s1 strain of *H. pylori* than the *vacA* type s2 strain (P=0.075). With the allelic variation in the m region of the *vacA* gene, no relation with the cure rate was observed. It was suggested in 1997 that (20):

> "Physicians who want to treat individuals without an ulcer should expect lower cure rates than those reported in the published research. In the coming years patients with FD could well need treatment for 10-14 days, whereas patients with ulcers could be treated successfully in just 7 days."

In the present article, data published since these first observations are discussed.

### DIFFERENT CURE RATES IN PUD AND FD: CLINICAL DATA

Over the past five years, many studies, mainly using PPI triple therapy, have demonstrated a higher cure rate in PUD patients than that in FD patients. A typical 5% to 15% difference in cure rate between PUD and FD is usually found, but bigger differences have also been reported. The difference is of clinical significance given the observation that cost effectiveness is mainly determined by efficacy (2). A number of these studies are shown in Table 1 (19,21-39). There is homogeneity in the data; antimicrobial resistance and smoking are factors that need to be considered. Some other studies did not document a difference between PUD and FD (34,40-47). However, if the overall cure rate in a study is high, it is difficult to reach significance for individual prognostic variables, especially in studies with a limited sample size. Studies with a lower overall cure rate are, therefore, more likely to report a difference in efficacy.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>n</th>
<th>Therapy regimen</th>
<th>Rate of cure for peptic ulcer disease (%)</th>
<th>Rate of cure for functional dyspepsia (%)</th>
<th>Difference (%)</th>
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<td>van der Hulst et al (19)</td>
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<td>PPI-Amox dual</td>
<td>79</td>
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<td>RBC-triple</td>
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<td>84 (NS)</td>
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*Statistically significant. Amox=Amoxicillin; BIS=Bismuth; NS=Not significant; PPI=Proton pump inhibitor; RBC=Ranitidine bismuth subcitrate*
More importantly, we know of only one study that showed an opposite result (48). In this study, patients with gastric ulcer had a significantly lower cure rate than those with duodenal ulcer or FD. In other studies, however, patients with gastric ulcer were easier to cure (32,33). Presently, there is no reason to consider duodenal and gastric ulcer patients separately. Based on these data, it can be safely concluded that the difference between PUD and FD is real, and that it is of clinical significance.

**DOES BISMUTH HAVE AN ADVANTAGE IN PATIENTS WITH FD?**

One wonders if the difference in cure rates between PUD and FD occurs with all treatment regimens or whether the phenomenon is confined to certain regimens. For quadruple therapy a difference in efficacy between PUD and FD was only documented in one- and two-day studies, but never in studies lasting more than four days. Either the regimen is so effective that it cures all FD patients, or the bismuth selectively improves the performance in the FD subgroup. In a large Spanish study, Gisbert et al (29) did not observe a difference in cure rate between PUD and FD patients treated with ranitidine bismuth subcitrate (RBC), and amoxicillin and clarithromycin, but did find a difference with PPI triple therapy. RBC triple therapy was superior to PPI triple therapy only in the FD subgroup (29). This effect remained in a multivariate analysis, thus neutralizing effects such as age, sex and smoking. The authors (29) implied that RBC triple therapy should be preferred over PPI triple therapy, especially when treating FD patients. Some criticism was raised surrounding these data (49). According to a meta-analysis, RBC triple therapy, with clarithromycin and an imidazole, appears to be superior to PPI triple therapy with the same antibiotics (50). Bismuth could theoretically have an advantage over PPIs in a noninflamed mucosa and help the antibiotics to reach the bacteria. Bismuth appears to be especially beneficial in areas with a high rate of resistance and also in more therapy resistant FD cases. The pharmacokinetics of bismuth in inflamed and noninflamed mucosa need further study (51,52).

**BIOLOGICAL EXPLANATION FOR THESE FINDINGS**

To accept the observed differences, we need a sound biological explanation and we need to explain why the cure rate is higher in PUD than FD patients. This cannot be explained by a difference in compliance, but the environment inside the stomach may be different between these clinical entities. It is believed that differences in the infecting strains of *H pylori* provide the most likely explanation. Apart from the data (19,20,39) described above, a meta-analysis has confirmed that more virulent strains (vacA s1, cagA-positive) are easier to eradicate than less virulent strains (vacA s2, cagA-negative) (53). A risk difference of 14% was found after pooling the data. This difference remained within the group of PUD patients in whom it was most pronounced, as well as in the group of FD patients. Other authors have reported similar findings (54). But what is the mechanism? There is no correlation between virulence factors and antimicrobial resistance. Interestingly, it appears that less virulent strains reach higher densities in the mucosa (55) and, as shown in several studies, it is more difficult to cure a patient with a high bacterial load (56,57). The more virulent strains, on the other hand, cause more inflammation (58-61). The increased inflammation may facilitate the delivery of the antibiotics to the site of bacterial colonization (39). Several studies have shown that patients with more inflammation had a higher probability of being cured of *H pylori* infection (32,48,62), an observation that further supports the hypothesis of different susceptibilities to antibiotics for different infecting strains. PUD patients are more often infected with virulent strains than FD patients (59,63-65), and this may explain the difference in cure rates between PUD and FD.

**WHAT ARE THE CLINICAL IMPLICATIONS OF THIS OBSERVATION?**

Several years ago, treatment studies included only ulcer patients, whereas more recent studies usually include only FD or a mix of cases. Based on a 5% to 15% difference in cure rates, it is clear that the selection of study patients may have a considerable impact on the overall cure rate. Most published meta-analyses have simply pooled the data for a particular antibiotic regimen and have usually disregarded any difference between PUD and FD cases. This may explain why the cure rates in more recent studies come out lower than earlier studies and why the results of eradication in everyday practice appear to be lower than documented in the literature. In primary care, as well as in secondary care, more patients with FD are being treated every year, especially when ‘test and treat’ strategies are being used in patients with uninvestigated dyspepsia. With the seven-day triple therapies physicians must realize that cure rates fall below 80% in FD, and this necessitates testing and retreated large groups of patients. Secondary resistance is already becoming a rather serious clinical problem (3,66). Testing for cure in all patients and retreatment those who failed with quadruple therapy, as suggested by the Maastricht 2000 consensus (4), will assure eventual cure of the infection in the majority of patients, but it will increase the workload of physicians. Selectively replacing PPI triple therapy with the more effective seven-day quadruple therapy in patients with FD may help, but it will take more time to explain and motivate the patient.

Another way to deal with the decreased efficacy of antibiotic therapy in patients with FD is to use the same therapy with a different treatment duration in PUD and FD patients. It may be sensible to prolong treatment in patients with FD who have a higher probability of being infected with a less virulent, but more resistant strain of *H pylori*. The Maastricht consensus (4) advises triple therapy with either a PPI or RBC for at least seven days. It is known from the literature that the cure rate can be increased by 3% to 9% by increasing the treatment duration from seven to 10 to 14 days (67). Therapy can remain at seven days for patients with a documented ulcer. When using the ‘test and treat’ approach in patients with uninvestigated dyspepsia, the physician must assume that most patients will suffer from FD. In that clinical situation it is logical also to use prolonged antibiotic therapy. Eradicating *H pylori* in uninvestigated dyspepsia or FD patients is a clinical challenge. Decision analysis has shown that the costs of therapy are less important than the overall cure rate (2). Paying for extra days of treatment is therefore compensated by not having to retreat a certain percentage of patients. Only one study has shown that increasing the treatment duration of
PPI, amoxicillin and clarithromycin from six to 12 days was required in FD, but not in PUD patients (35). Guidelines in the United States advise a 10- to 14-day treatment period in all cases. I believe that consideration should be given to abandoning the ‘one treatment for all’ strategy and that instead the treatment duration should be adjusted according to the known prognostic factors and bacterial sensitivities if available. FD patients are more difficult to cure than PUD patients,

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cagA and vacA status for the efficacy of antibiotic treatment.


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