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

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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 (virulent [*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*

La thérapie par éradication devrait être différente pour les patients dyspeptiques que pour les patients ulcéreux

Les médecins devraient tenter d'obtenir un taux de guérison optimal avec leur thérapie initiale par éradication de l'*Helicobacter pylori*. La plupart des médecins utilisent le même traitement pour tous leurs patients. L'infection à *H pylori* chez les patients atteints d'ulcère peptique (UP) est plus susceptible d'être guérie que chez ceux qui sont atteints de dyspepsie fonctionnelle (DF). Des différences de taux de guérison de 5 % à 15 % sont généralement déclarés, ce qui est considéré comme pertinent d'un point de vue clinique. D'après une explication biologique plausible de cette observation, diverses souches (virulentes [*cagA+, vacA*, type s1] par rapport aux non virulentes [*cagA-+, vacA*, type s2]) en cas d'UP et de DF induisent divers changements de la muqueuse gastrique, ce qui facilite l'efficacité antimicrobienne ou lui nuit. Les médecins devraient savoir que la plupart des études de traitement publiées n'incluent que des patients atteints d'UP. Ainsi, en pratique clinique, le taux de guérison obtenu chez les patients atteints de DF ou, peut-être, de dyspepsie non explorée, est généralement plus faible que celui qui est déclaré dans la documentation scientifique. Cette constatation a des répercussions sur le choix du traitement. Les médecins devraient prolonger la durée de la thérapie initiale par éradication des espèces d'*Helicobacter* de sept à 10 à 14 jours chez les patients sans ulcère.

Curing *Helicobacter pylori* infection in patients with ulcer disease improves their quality of life and decreases health care costs (1). Regimens with the highest cure rates are also the most cost effective (2). Retreatment after a failed earlier attempt is more difficult and expensive (3). Therefore, physicians should try to achieve an optimal cure rate in their initial treatment attempts.

Studies show a wide range of cure rates with the use of the same *H pylori* eradication regimens. This demonstrates that in a clinical study, many factors, apart from the selected regimen (choice of drugs, total daily dose, dosing schedule, intake in relation to meals, formulation, pretreatment with acid suppressants, etc), determine the outcome of antibiotic therapy. These are related to the patient (compliance, age, weight, polymorphism of CYP2C19, ethnicity, smoking habits, status of the gastric mucosa, bacterial density, etc), the infecting strain of *H pylori* (bacterial properties, antimicrobial resistance) and the study design of the trial. Only some of these factors can be controlled by the physician. For example, a thorough explanation to the patient may improve compliance.

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 (4). The choice of drugs is usually dictated by costs and the background rate of antimicrobial resistance and may, therefore, vary around the world (5). 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 (6-8). 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 (4). 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

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TABLE 1
Overview of *Helicobacter pylori* eradication studies which documented a difference in cure rates between patients with ulcer disease and those with functional dyspepsia

Author (reference)	n	Therapy regimen	Rate of cure for peptic ulcer disease (%)	Rate of cure for functional dyspesia (%)	Difference (%)
van der Hulst et al (19)	155	PPI-Amox dual	79	58	21
Catalano et al (21)	115	PPI-triple	92	60*	32
Luna et al (22)	48	PPI-triple	93	68*	25
Houben et al (23)	252	PPI-triple	91	82*	9
Zullo et al (24)	360	dual/triple	86	57*	27
Takats et al (25)		PPI-triple	91	83	8
Katicic et al (26)	857	PPI-triple	79	65*	14
Borda et al (27)		PPI-triple	82	73*	9
Broutet et al (28)	2751	PPI-triple	78	66*	12
Gisbert et al (29)	297	PPI-triple	88	59*	29
	79	RBC-triple	86	84 (NS)	2
	105	RBC-triple	100	87*	13
Olafsson et al (30)	183	RBC-triple	97	86*	11
Xiao et al (31)	892	PPI/BIS-triple	79	73*	6
Labenz et al (32)	423	PPI-Amox dual	79	45*	34
Moreno et al (33)	450	Dual	63	46*	17
Pieramico et al (34)	148	PPI-Amox dual	62	47*	15
Hermida et al (35)	364	PPI-triple	82	66*	16
Gutierrez et al (36)	106	PPI-triple	92	84	8
Tucci et al (37)	71	2-day quadruple	94	74*	20
De Francesco et al (38)	225	several	85	73*	12
van Doorn et al (39)	71	1-2-day quadruple	76	54*	22

**Statistically signficant. Amox Amoxicillin; BIS Bismuth; NS Not significant; PPI Proton pump inhibitor; RBC Ranitidine bismuth subcitrate*

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 *cag*A-positive *H pylori* strain (73% versus 52%) than patients with a *cag*A-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 *vac*A allele (P=0.007). Patients with peptic ulcers were more frequently positive for *cag*A and the *vac*A s1 allele than patients with FD (P=0.146 and P=0.012, respectively). A higher cure rate was found for the more pathogenic *vac*A type s1 strain of *H pylori* than the *vac*A type s2 strain (P=0.075). With the allelic variation in the m region of the *vac*A 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.

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 retreating large groups of patients. Secondary resistance is already becoming a rather serious clinical problem (3,66). Testing for cure in all patients and retreating 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, and a longer primary treatment is one way to deal with that reality. Physicians should adopt routine testing for cure with a noninvasive test, as recommended by the Maastricht consensus (4). Physicians can thus monitor their own overall eradication results. If these results are below 90% (2), adjusting treatment duration as recommended above is the first option, and choosing another more effective initial therapy is the second.

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