Clinical aspects in Helicobacter pylori infections

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Summary

Since the recognition of *Helicobacter pylori* in 1983, there has been a revolution in the understanding and clinical management of peptic ulcer disease. Peptic ulcer disease was previously considered a chronic, relapsing condition of unknown cause in which psychological stress and abnormalities in gastric acid secretion were thought to play a fundamental role. Diets, antacids and bed rest or surgery were the treatments of choice for peptic ulcer disease until the 1970s, when more effective medical therapies became available. Now, peptic ulcer disease has been shown to be a chronic, specific and curable infectious disease.

The discovery of the association of *H. pylori* with peptic ulcer disease led to the development of effective therapies that eradicate the bacterium and cure the disease. Most anti-*H. pylori* therapies consist of an acid inhibitor (most often, a proton pump inhibitor) and/or bismuth or ranitidine bismuth citrate in combination with one or two antimicrobials (e.g. metronidazole, tetracycline, clarithromycin and amoxycillin). Combinations of these medications are necessary to eradicate *H. pylori*. Current therapies are now achieving successful eradication in over 80% of patients. Unfortunately, this therapeutic advance has been rather empirical and lacking in scientific basis, so that when treatment fails, the underlying reasons remain unclear. Therefore the final arbitrator on the efficacy of certain regimens or the effect of specific factors on eradication rates must come from clinical trials. Several factors that (may) play a role in the efficacy of eradication therapy have been the subject of this thesis.

In Chapter 1 an overview is given of the current knowledge on *H. pylori*, related to the subjects that were studied in this thesis.

In Chapter 2 we studied whether metronidazole resistance affects the *H. pylori* eradication rates in 122 patients treated with proton pump inhibitor (PPI)-based triple therapies. PPI-triple therapies are extremely effective in eradicating *H. pylori*, with cure rates of more than 95%, reported in the MACH1 study. Therefore, the hypothesis was made that the proton pump inhibitor omeprazole could overcome metronidazole resistance, and a PPI triple therapy containing metronidazole (OCM: omeprazole-clarithromycin-metronidazole) was equally effective as a non-metronidazole-containing PPI triple regimen (OAC: omeprazole-amoxycillin-clarithromycin). We found that one-week OAC and OMC treatments were equally effective therapies in patients with metronidazole-susceptible *H. pylori* strains. However, using the OMC regimen, neither equality nor significant differences could be shown between patients with metronidazole-resistant or -susceptible *H. pylori* strains.

In infectious diseases antimicrobial resistance is, in general, an important factor that leads to therapy failure. With *H. pylori* this is not always evident, and Méraud stated in 1997 that 'there is no situation where the clinical relevance of antimicrobial resistance detected in-vitro is more controversial than *H. pylori* resistance to nitroimidazole compounds'.
In trying to resolve the conflicting data in the literature on the impact of antimicrobial resistance on *H. pylori* eradication rates, we systematically reviewed all *H. pylori* eradication trials, published in full paper or abstract. (Chapter 3). This review, designed and conducted with the utmost attention to exclude all possible bias, involved almost 40,000 treated patients out of 1,091 study arms and comprises the largest database on *H. pylori* eradication trials published to date. With this review we could demonstrate a highly significant drop in efficacy of bismuth- and PPI-based triple therapies in the case of nitroimidazole resistance. For quadruple therapy and ranitidine bismuth-based therapies more data are needed to definitely establish the clinical relevance of detecting nitroimidazole resistance *in vitro*. In the case of clarithromycin resistance, the efficacy of most clarithromycin-containing regimens is substantially decreased, however data are still scarce.

Several factors contribute to the many conflicting results found in the literature regarding the impact of antimicrobial resistance. For example, standardization of testing of antimicrobial resistance is needed to improve comparison among trials. Despite the drawbacks, finding resistant strains *in vitro* has shown to reflect a real phenomenon *in vivo*, and can predict a drop in efficacy of most anti-*H. pylori* regimens.

*H. pylori*-cure rates may vary in different geographical regions. This may be caused by differences in the hosts or, considering the enormous heterogeneity of *H. pylori* and its geographical differences in strains, also by differences in *H. pylori* strains. Because of these regional differences in cure rates, several authors have stated that the efficacy of anti-*H. pylori* regimens should be confirmed in a given geographical area before their use can be promoted in that area. Therefore, in Chapter 4, we reviewed all published anti-*H. pylori* therapy trials performed in The Netherlands. Bismuth-based triple therapies have been scarcely studied in The Netherlands and show inadequate eradication rates of below 80% on an intention-to-treat basis. An exception is bismuth-tetracyclin-metronidazole triple therapy given for two weeks that was studied in five study arms, involving over 300 patients, and that appeared highly efficacious. Both quadruple therapy and ranitidine bismuth citrate-based therapies have been studied on a relatively large scale in The Netherlands and both appear to be very effective. PPI-triple therapies, although the most studied anti-*H. pylori* therapy world-wide, have been studied in relatively few patients in The Netherlands, yet indicate adequate cure rates of over 80% on an intention-to-treat basis. All regimens, except omeprazole-clarithromycin-metronidazole given for one week, showed a trend to a lower efficacy in the case of metronidazole resistance; this was, however, only significant for bismuth-tetracyclin-metronidazole combination therapy for one or two weeks. Data on clarithromycin resistance in The Netherlands are too limited to draw final conclusions.

Another factor that may play a role in the effectiveness of eradication therapy is the clinical expression of the infection. In Chapter 5, a large clinical trial involving 317 patients is described, showing a significantly higher efficacy of PPI triple therapy in patients with past or present peptic
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ulcer disease, compared to those with functional dyspepsia. We also showed that this difference in efficacy cannot be explained by differences in compliance, antimicrobial resistance, gender, or type of PPI triple therapy. It has been shown that differences in *H. pylori* resistance can lead to different clinical outcomes. Our study suggests that more virulent strains, present in patients with ulcer diathesis, are more susceptible to antimicrobial therapy.

*H. pylori* infection is usually diagnosed via endoscopically-obtained biopsies. A non-invasive test is preferred over a biopsy-based test to check for cure of the infection. Urea breath tests have been found reliable to test for the presence of *H. pylori* infection before therapy; however, relatively few data exist on the accuracy of breath testing to test for cure of an *H. pylori* infection. A drawback of urea breath tests has been the requirement of expensive and complex instrumentation. In Chapter 6 we studied the sensitivity and specificity of the Laser Assisted Ratio Analyzer (LARA™) 13C-urea breath test to test for cure of an *H. pylori* infection. The LARA™ system is a fully automated device which contains two carbon dioxide lasers that measure the ratio of 13-carbon to 12-carbon with an extremely high precision, based on a novel technology called laser optogalvanic effect spectroscopy. This study was performed in collaboration with Dr. D. Vaira from Bologna, Italy, and involved a total of 181 patients. The urea breath test was shown to be reliable in monitoring cure of an *H. pylori* infection and the LARA™ breath test proved to be easy to handle without the need for a trained technician. The 13C-urea breath tests may well become the test of choice in confirming cure of an *H. pylori* infection, because it is safe and convenient for the patient, highly accurate, easy to use, and relatively cheap.

PPI triple therapies are the most frequently recommended eradication regimens world-wide with a well-documented efficacy. However, when an initial PPI triple regimen fails, little is known on the efficacy of second-line eradication regimens. In Chapter 7 a trial is described where patients who failed a PPI triple therapy were randomly allocated to a second line omeprazole-metronidazole-clarithromycin therapy or a quadruple therapy, both given for one week. This study showed a significantly higher efficacy of 85% for the second-line quadruple treatment, compared to 22% for the PPI triple therapy. Seven patients failed the second-line PPI triple therapy and were retreated with a third-line quadruple therapy, showing an eradication rate of 71%. Failure of these regimens led to the development of secondary resistance to clarithromycin in 33% and, for metronidazole, in 45% of the patients.

Antimicrobial resistance can partly explain the treatment failures in our study. However, other factors that may be related to the host, to the pharmacology and pharmacodynamics of the therapy, to characteristics of the gastric mucosa or to differences in *H. pylori* strains may also play a role. These `other' factors, currently not well understood, can explain why some *H. pylori* seem "ineradicable", or why certain patients, who appear motivated and compliant and show no antimicrobial resistance to any of the antibiotics used, still fail sequential anti-*H. pylori* therapies.

Finally this thesis is summarized in Chapter 8.
In conclusion, in this thesis several primarily clinically-based questions, related to the antimicrobial therapy in *Helicobacter pylori* infections, have been studied. These studies can help clinicians in treating patients with *H. pylori* infections to choose better therapies to eradicate *H. pylori* and decide what to do in case of therapy failure.

Despite the enormous amount of effort and the number of studies that have been done in the field of *H. pylori*, there is still a long way to go. We are just at the beginning of understanding the microbiology of *H. pylori* with its tremendous strain-to-strain variability. We still do not know how *H. pylori* are transmitted. What are the host factors that place an individual at risk for *H. pylori*-associated disease? The role of *H. pylori* in functional dyspepsia is still controversial. We do not know the role of *H. pylori* in NSAID-related ulcer disease. There is discussion regarding the role of *H. pylori* in gastric cancer and whether eradication of this bacterium will reduce the risk of developing gastric adenocarcinoma. We still do not have the magic bullet that kills all *H. pylori*. The increase of resistance rates against common anti-*H. pylori* drugs emphasizes the need for novel drugs. Also, the role of *H. pylori* infection in several extra-intestinal diseases is an ongoing discussion in the literature. Vaccines will probably be developed, but how and when and where they should be used remains unsettled. Indeed, we do not know ‘if the only good Helicobacter is a dead Helicobacter’; in other words, we do not know if there are patients who benefit from an *H. pylori* infection. Recently, possible protective effects of *H. pylori* for refluxoesophagitis and for the development of adenocarcinomas in the gastric cardia were suggested. There may be other, as of yet unidentified, beneficial effects of *H. pylori* infections.

Furthermore, considering that *H. pylori* has survived for so many millennia in the human stomach, and considering the enormous amount of bacteria that exist (in the range of 10^7 to 10^11 in the stomach of one human being), this bacterium is likely to be a survivor. We have already seen that *H. pylori* have several means of self-protection (e.g., the emergence of secondary resistance) and has been shown to be difficult to eradicate. We may well become increasingly impressed by the ‘tricks’ *H. pylori* have to escape eradication or, in other words, to survive.

To answer these and many other remaining questions we need rigorously designed studies with large numbers of patients, with uniform therapies and methods of testing *H. pylori*, and with data on the effectiveness of different therapies separately for sensitive and resistant organisms. Only then can different studies be compared and evaluated.

As in other important infectious diseases, community surveillance of antimicrobial resistance against *H. pylori* infections should be performed. If antibiotic resistance increases further, pre-therapy antibiotic sensitivity testing on an individual basis may become necessary.