H. pylori eradication marks a historical milestone in the cure of peptic ulcer disease, and indications for other H pylori-associated clinical conditions are now expanding to include the possible prevention of gastric cancer in select populations at risk (1,2). H pylori eradication therapies are complex, therefore, the increased use of these treatments demands careful consideration of the factors responsible for treatment failure. A multitude of pioneering studies aimed at identifying the most effective regimens have contributed largely to promoting several different treatment regimens and schedules with low failure rates. It is now the accepted standard (corroborated by appropriate guidelines) that only therapeutic regimens tested in appropriate trials with an efficacy in eradication of more than 80% should be recommended for clinical practice (1,2).

For recommended therapies, the following factors have been identified as contributing to treatment failure: compliance, antibiotic resistance, disease entity associated with the H pylori infection, bacterial virulence factors and pharmacological properties (Table 1).

**Key Words:** Antibiotic resistance; Helicobacter pylori; Treatment failure

**Compliance**
Compliance is a crucial element for successful H pylori eradication. The complexity of the treatment regimen and a number of even minor side effects (ie, mild diarrhea, abnormalities in taste sensation, etc) may either simply lead to inadequate intake of the prescribed doses or induce patients to interrupt the therapy before reaching the minimal required duration of 7 days. Data on the impact of compliance derive from subanalyses of treatment trials. Whereas the negative influence of noncompliance was clearly apparent in early complex treatment regimens such as Bismuth-based triple or quadruple therapies (3-5), the current standard proton pump inhibitor (PPI)-based triple therapies with tablets prescribed twice daily confer good compliance that rarely leads to treatment discontinuation (6,7). The most widely accepted threshold for sufficient compliance is now stated as the intake of at least 90% of the prescribed tablets.

Indirect indications of the role of compliance comes from recent field studies (8-10). Studies evaluating eradication rates...
in primary care have repeatedly shown that eradication rates are about 10% to 20% lower compared with previous clinical trials. The reasons for this phenomenon may be many, but differences in compliance are most likely an important factor.

In practice, the clinician often confronts the problem of whether patients experiencing adverse events should be encouraged to continue their treatment. Hence, this problem is linked to the concept of the minimal efficacious treatment duration. Most studies, which have been aimed at shortening treatment duration to less than one week, failed to prove efficacy equivalence with the one week regimens (11). The negative impact of microbial resistance is increased by shortening the treatment duration, and this is particularly so for the nitroimidazoles (12).

Therefore, the first challenge for the physician is to dedicate time to a careful explanation of the therapeutic regimen and to obtain the optimal acceptance and compliance of patients. The patient should learn before starting treatment what symptoms they may experience, which symptoms are harmless and of no concern (eg, taste disturbances, loose stools, etc) and which symptoms should lead to further consultation (eg, malaise, diarrhea).

Antibiotic resistance

Antibiotic resistance is the primary cause of treatment failure besides poor compliance. Antibiotic resistance concerns mainly two of the major antibiotic components in current eradication regimens: macrolides and nitroimidazoles. Within the group of macrolides there is almost 100% cross-resistance between different compounds, including clarithromycin, azithromycin and roxithromycin (13). The same applies for the two principal nitroimidazoles: tinidazole and metronidazole.

Although the results of in vitro testing for resistance are statistically associated with treatment failures, the predictive value of resistance testing for the selection of a specific therapy is limited (14). Several reasons contribute to this low predictive value of resistance testing. First, in a proportion of patients, resistance can be overcome by the synergy of two or more antibiotics (15). Second, co-medication with a PPI (6,15) and/or bismuth compounds (16) reduces the negative impact of resistance. Third, the in vivo conditions of the bacterium-antibiotic interaction differ from those of in vitro conditions, particularly in terms of acidity and antibiotic concentrations within the gastric mucus and gastric mucosa (6,17,18). Finally, some data indicate that resistance acquired during treatment failure (‘secondary resistance’) is of greater importance than pre-existing resistance (‘primary resistance’) (19,20).

The relative impact of in vitro resistance is different for nitroimidazoles, which is easily overcome, and macrolides, which is more difficult to overcome. Nitroimidazole resistance reduces the efficacy of PPI-clarithromycin-nitroimidazole triple therapy to about 70%, of PPI-amoxicillin-nitroimidazole triple therapy to about 60% (12), and of ‘classic’ triple therapy (bismuth salt, metronidazole, tetracycline) to 50% to 75% (5), depending on the treatment duration (one versus two weeks). The lowest adverse impact of nitroimidazole resistance is seen with the so called quadruple therapy (ie, PPI, bismuth salt, metronidazole, tetracycline), which achieves an eradication rate of about 80% in nitroimidazole-resistant strains (12). All these figures represent per protocol data and compare with an approximate 90% eradication rate for infection with susceptible strains (12).

Clinical data on the impact of nitroimidazole resistance are subject to considerable variation. One important confounding factor is the methodology used for nitroimidazole resistance testing. Compared with the agar dilution test as the gold standard, the ellipsometer test seems to overestimate the prevalence of nitroimidazole resistance, whereas the agar diffusion test is inadequate for this indication. The prevalence of pre-treatment resistance reflects the frequency of previous antibiotic use for other indications. For nitroimidazoles, it amounts to about 80% in tropical regions where these drugs are frequently used for diarrhea (21). In countries with a moderate climate the prevalence of resistance varies mainly between 7% and 60% (22-25). Women have a one-third higher risk of harbouring nitroimidazole-resistant strains.

The prevalence of macrolide resistance is limited to between 1% and 3% in most of the countries (22-25). It is higher (greater than 10%) in several countries including France, Spain, Portugal, Japan and the USA, with a tendency to an increasing trend. It is noteworthy that while the prevalence of clarithromycin resistance in the adult population in Germany is 2% to 3% (25), in children the prevalence has been reported to be as high as 20% in Munich (S Koletzko, personal communication), and in Portugal as high as 44% (25,26). The impact of macrolide resistance is more serious, reducing the eradication rate to under 50% (27).

For the selection of a second-line treatment, the emergence of post-treatment resistance is an important aspect. Post-treatment resistance is observed with macrolides in more than 50% of cases, whereas for nitroimidazole the rate comes close to 100%. After PPI-metronidazole-clarithromycin therapy, we (20) and others (28) frequently observed the development of dual resistance leading to a low eradication rate with any second-line treatment containing a macrolide or nitroimidazole (29). Therefore, the selection of the first-line therapy should take into account the options for a second-line treatment. An appropriate approach is to use PPI-clarithromycin-amoxicillin therapy as a highly effective first-line treatment, which can be followed, in case of failure, by quadruple therapy (Figure 1). This package concept avoids repeating an antibiotic with the potential for post-treatment resistance (2). If, however, the prevalence of macrolide resistance is high (greater than 20%), the best choice for first-line treatment is probably quadruple therapy (30). Local and regional variations must also be considered. In some countries, bismuth salts are not approved or even not available. Furthermore, the prevalence of resistance varies widely. Regional studies should provide data on the current preva-
What constitutes failure of H pylori eradication therapy?

Table 2

<table>
<thead>
<tr>
<th>Result of testing for resistance</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitroimidazole-susceptible</td>
<td>PPI-clarithromycin-amoxicillin</td>
</tr>
<tr>
<td>Macrolide-susceptible</td>
<td>or PPI-clarithromycin-metronidazole</td>
</tr>
<tr>
<td>or PPI-clarithromycin-metronidazole-tetracycline</td>
<td></td>
</tr>
<tr>
<td>Nitroimidazole-resistant</td>
<td>PPI-clarithromycin-amoxicillin</td>
</tr>
<tr>
<td>Macrolide-susceptible</td>
<td>PPI-bismuth-metronidazole-tetracycline</td>
</tr>
<tr>
<td>or PPI-amoxicillin-metronidazole</td>
<td></td>
</tr>
<tr>
<td>Nitroimidazole-susceptible</td>
<td>PPI-bismuth-metronidazole-tetracycline</td>
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</tr>
<tr>
<td>or PPI-amoxicillin-metronidazole</td>
<td></td>
</tr>
<tr>
<td>or PPI-amoxicillin-fluoroquinolone</td>
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</tbody>
</table>

PPI Proton pump inhibitor

Figure 1) Helicobacter pylori therapy: proposed algorithm for first-line treatment and further options in case of failure. PPI Proton pump inhibitor; RBC Ranitidine bismuth citrate

Disease entities

Disease entities associated with H pylori infection have been recognized to influence treatment efficacy. Peptic ulcer patients tend to respond better to eradication therapy than patients with functional dyspepsia. The difference is significant but of minor clinical importance. In patients with gastric mucosa-associated lymphoid tissue (MALT) lymphoma, response rates to eradication therapy are highest. It is notable that the higher the intrinsic efficacy of therapy, the smaller the differences among disease entities occur. These different expressions of disease, however, may only be a surrogate marker for important host and bacterial factors which may determine the degree of inflammation. It is well known that the proportion of strains expressing the genomic pathogenicity island, designated cag-PAI or cytotoxin-associated gene A (cagA), is higher in patients with peptic ulcer disease, gastric adenocarcinoma or gastric MALT lymphoma (39).

In patients with gastric mucosal atrophy and/or intestinal metaplasia, the proportion of cagA-positive strains is also higher. In the late stages of gastric cancer, H pylori is often no longer detectable by direct tests, whereas cagA antibodies may still be detectable. These patients usually have reduced acid secretion that is influenced not only by the bacterial strains but also by genetic polymorphisms of interleukin-1-beta (40). Because eradication regimens require a certain amount of acid inhibition, in these conditions of low acid output eradication success is facilitated.

Bacterial virulence factors

To date, the best understood virulence factor is cagA. In the presence of this toxin, various cytokines such as interleukin-1 and interleukin-8 are upregulated (41,42). Depending on host factors, they eventually lead to direct acid inhibition or enhance the effect of acid suppressive drugs such as PPIs. Numerous studies have shown that without concomitant acid suppression, the efficacy of clarithromycin or amoxicillin is much reduced (43). Therefore, the presence of cagA-positive strains can increase responsiveness to therapy. We have investigated this issue (44) by performing a review of the surprisingly few studies (45-52) that reported an outcome of eradication rates depending on cagA status. The eradication rates were better in patients with peptic ulcer disease than with functional dyspepsia, the main difference being determined by cagA status (Table 3). With less effective therapies such as dual therapy, cagA-positive carriers have a better response to eradication therapy. This difference is less pronounced but still observed even with the more potent PPI based standard eradication regimens. Other virulence factors such as bab-A, vac-A and ice-A have not been found to be linked to treatment failures. Recently it has been reported that outer-inflammatory protein A (oip-A) correlates with bacterial density in a mouse model (51). Further investigations show that, besides the induction of proinflammatory responses, this virulence factor may even be more important than cagA (54). There is uncertainty at present whether the 35kD band on the immunoblot test does indicate a functionally active oip-A, or whether it may serve simply as a surrogate marker for oip-A. The presence of this band has...
been linked to treatment failure in a recent study and this may be due to a higher bacterial density (49). In summary, because cagA is a major trigger for the inflammatory response and oip-A is probably the trigger for colonisation, these bacterial 'attributes' appear to be important influencing factors for the response to antibiotic treatment.

Pharmacological properties

The pharmacological properties of drugs used for H pylori eradication treatment also deserve some attention. It has been shown that PPI treatment increases systemic absorption of bismuth, clarithromycin and amoxicillin. PPI treatment also increases the local availability of clarithromycin in gastric mucus by altering viscosity and favouring active transfer of the antibiotic from the mucosal site in the soluble mucus compartment (35). Cytochrome P450 (CYP) 2C19 polymorphisms are responsible for differences in PPI metabolism, and extensive or poor metabolizers have a lower degree of acid inhibition than intermediate or poor metabolizers (56-58). These differences are especially important in the Asian populations where the frequency of CYP 2C19 polymorphisms may be found in up to 15% of the population. Advanced age may additionally contribute to altered drug metabolism. Older age affects drug metabolism directly (ie, clarithromycin, PPI) and indirectly via decreased renal function (amoxicillin) but despite the higher systemic availability of drugs a relevant impact on H pylori eradication is not observed consistently in the elderly (49,59). Finally, the dose and duration of clarithromycin is of importance in the recommended standard PPI triple regimens. If clarithromycin is administered together with amoxicillin, 500 mg of clarithromycin twice daily is necessary, whereas in combination with metronidazole, 250 mg of clarithromycin twice daily is sufficient (60). There have been supportive data that the critical dose of metronidazole is 400 mg twice a day. With other multidrug regimens the dose may need to be increased to 400 mg three times daily (43, 61).

Other factors

Various other factors, such as age, sex and exogenous factors such as smoking have been identified in some studies to influence the success of H pylori eradication therapy. With the use of the optimized standardized current therapies, these factors no longer appear to be critical variables in the success of the therapy.

CONCLUSION

Knowledge of the recognized and well-documented factors that impact on therapy failures constitutes the ingredient for tailoring the individual therapy to be selected among the current standard options for H pylori eradication. The evolution and improvement of H pylori eradication therapies to the current standard are the results of the many lessons we have learned from eradication failures.

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What constitutes failure of *H. pylori* eradication therapy?


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