What constitutes failure for *Helicobacter pylori* eradication therapy?

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Apart from patients with peptic ulcer disease, the use of eradication therapy for *Helicobacter pylori* infection has been extended to patients with *H pylori*-positive dyspepsia and conditions at risk for gastric cancer. Standard treatments comprise a proton pump inhibitor plus two antibiotics for at least one week. The main factors leading to treatment failure are noncompliance and antibiotic resistance. Provided the patient is sufficiently informed about possible side effects, discontinuation of the newer triple therapies has become rare. The prevalence of antibiotic resistance varies considerably among different geographic regions, reflecting the habits of prescription of these antibiotics for other indications. Largely, it ranges from 1% to 15% for macrolides, and from 7% to 60% for nitroimidazoles. With nitroimidazole resistance, treatment failure occurs in only less than 50%; with macrolide resistance, by contrast, in more than 50% of the cases. Futhermore, bacterial and host-related factors (Cag A virulence factor, grade of inflammation) contribute to eradication success. In case of treatment failure, post-therapeutic resistance is frequent. Important principles for the choice of second-line treatment are: not to repeat an antibiotic with potential post-therapeutic resistance, and to ensure sufficient acid suppression.

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

Qu'est-ce qui établit l'échec d'un traitement d'élimination d'*Helicobacter pylori*?

À l'exception des patients aux prises avec un ulcère gastroduodénal, on a étendu le traitement de l'éradication de l'infection à *Helicobacter pylori* aux patients souffrant de dyspepsie *H pylori* positive et d'affections posant un risque de cancer gastrique. Les traitements standards comprennent l'administration d'un inhibiteur de la pompe à protons en plus de deux antibiotiques, pendant au moins une semaine. Les facteurs principaux qui causent l'échec du traitement sont la non-observance du traitement et l'antibiorésistance. Comme le patient est suffisamment informé des effets secondaires éventuels, l'interruption des plus récentes trithérapies s'est raréfiée. La fréquence de l'antibiorésistance varie considérablement d'une région géographique à l'autre, en fonction des habitudes de prescription des mêmes antibiotiques pour d'autres indications. Dans une large mesure, elle varie de 1 % à 15 % dans le cas des macrolides et de 7 % à 60 % quant aux nitro-imidazoles. Dans le cas de la résistance à ces derniers, l'échec du traitement ne survient que dans moins de 50 % des cas; on observe par contre une résistance aux macrolides dans plus de 50 % des cas. En outre, les facteurs bactériens et liés à l'hôte (facteur de virulence Cag-A, degré d'inflammation) contribuent à la réussite de l'élimination. Dans les cas d'échec du traitement, la résistance après traitement est fréquente. Lors du choix d'un traitement de deuxième intention, il importe de respecter les principes suivants : ne pas répéter l'administration d'un antibiotique présentant un risque de résistance après traitement et assurer une diminution suffisante de l'acide.

Helicobacter 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 regimen 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).

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 seven 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

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TABLE 1
Causes for *Helicobacter pylori* treatment failure

- Insufficient patient compliance
- Antibiotic resistance
- Disease condition associated with *H pylori* infection (ie, functional dyspepsia < duodenal ulcer/gastric ulcer < mucosa-associated lymphoid tissue lymphoma)
- Bacterial factors (*cagA*-negative strains)
- Pharmacological properties (inadequate dose and/or duration for certain combinations)

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 pretreatment 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-

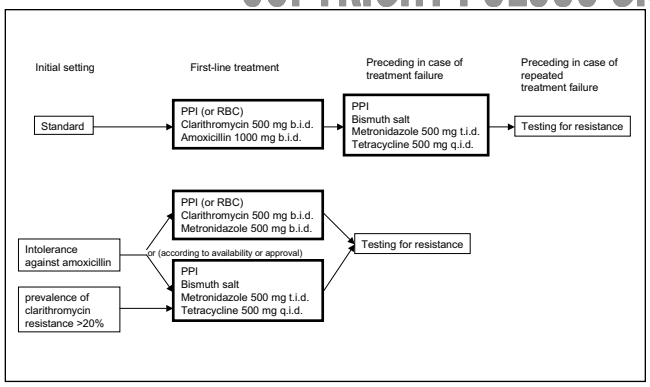

Figure 1) Helicobacter pylori *therapy: proposed algorithm for first-line treatment and further options in case of failure. PPI Proton pump inhibitor; RBC Ranitidine bismuth citrate*

lences rates for resistance, which should in turn form the basis for tailoring individual treatments.

Resistance against amoxicillin or tetracycline has been the subject of a few case reports and small series (22-24,32,32). These findings need to be confirmed by other laboratories. In most countries no such resistance has been reported, even after multiple treatment attempts. Nevertheless, after repeated treatment failure, resistance against these antibiotics should be determined. Furthermore, sentinel studies need to be performed.

The emergence of dual resistance against macrolides and nitroimidazoles still poses a difficult challenge for the selection of a second-line treatment (29) (Table 2). Quadruple therapy with PPI, bismuth salt, metronidazole and tetracycline is one option. However, nitroimidazole resistance emerging during treatment failure seems to have a greater negative impact on this treatment than a pretreatment resistance on first-line quadruple therapy (20). In some countries, metronidazole may be substituted by furazolidone; like nitroimidazoles, this is also a nitrofuran derivative, but reportedly with no cross-resistance (33). Experience with this drug is limited, but recent data suggest that nitroimidazole resistance is also linked to treatment failure with furazolidone (34). Several authors (20,35,36) report eradication rates of approximately 80% with high-dose PPI-amoxicillin, but these data are in contrast to the formerly reported worse results with dual therapy. Fluoroquinolones (37) or rifabutin (38), each in combination with amoxicillin and a PPI, have shown promising results, but have been evaluated only in a small number of patients. Treatment failure with these drugs also leads to acquired resistance.

TABLE 2
Options for retreatment dependent on in vitro resistance

Result of testing for resistance	Recommended therapy
Nitroimidazole-susceptible Macrolide-susceptible	PPI-clarithromycin-amoxicillin or PPI-clarithromycin-metronidazole or PPI-bismuth-metronidazole-tetracycline
Nitroimidazole-resistant Macrolide-susceptible	PPI-clarithromycin-amoxicillin
Nitroimidazole-susceptible Macrolide-resistant	PPI-bismuth-metronidazole-tetracycline or PPI-amoxicillin-metronidazole
Nitroimidazole-resistant Macrolide-resistant	PPI-bismuth-metronidazole-tetracycline PPI-bismuth-furazolidone-tetracycline or PPI-amoxicillin high dose or PPI-amoxicillin-rifabutin or PPI-amoxicillon-fluoroquinolone

PPI Proton pump inhibitor

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 differences among disease entities occur. These different expression 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 (53). 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 funtionally active oip-A, or whether it may serve simply as a surrogate marker for oip-A. The presence of this band has

TABLE 3
Pooled *Helicobacter pylori* eradication results according to *cagA* status and clinical diagnosis

	H pylori-negative	*H pylori*-positive	% cured
Nonulcer dyspepsia			
cagA-positive	200	31	86.6
cagA-negative	124	46	72.9
Peptic ulcer disease			
cagA-positive	122	11	91.7
cagA-negative	29	10	74.4

Data from references 45,46,48,49. cagA-*positive versus* cagA-*negative groups: NUD OR 2.4 (95% CI 1.4-4.0), P=0.0008 (Fisher´s exact test). PUD OR 3.8 (95% CI 1.5-9.9), P = 0.009 (Fisher´s exact test). Differences between* cagA- *positive NUD/PUD as well as* cagA-*negative NUD/PUD are not significant*

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 (55). Cytochrome P450 (CYP) 2C19 polymorphisms are responsible for differences in PPI metabolism, and extensive or rapid 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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