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Review article: the treatment of refractory Helicobacter pylori *infection*

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SUMMARY

The occurrence of refractory *Helicobacter pylori* infection is increasing. When the bacteria are not eradicated it means that the antibiotics have not reached the gastric mucosa at a sufficient concentration and over a sufficient time lapse to kill them. The main reasons for this are poor patient compliance, resistant bacteria, low gastric pH and a high bacterial load. Therefore, when administering a new treatment, it is important to choose antibiotics which do not face resistance problems and which increase the dosage of antisecretory drugs and the duration of treatment and, if possible, to add a topical agent such as bismuth salt.

The recommended empirical strategy is to prescribe quadruple therapy or, alternatively, 2-week triple therapy including amoxicillin–metronidazole, tetracycline–metronidazole or amoxicillin–rifabutin. However, when *H. pylori* is susceptible, clarithromycin can still be used. In the case of a high level of metronidazole resistance, furazolidone can be employed. In each case, it is important to ensure good patient compliance, and counselling is helpful in this regard. However, the best approach remains the prevention of refractory *H. pylori* infection and, for this purpose, antimicrobial susceptibility testing before first-line therapy is important and should be encouraged.

INTRODUCTION

The discovery of *Helicobacter pylori* heralded a breakthrough in the field of gastroenterology. Diseases, such as peptic ulcer disease, for which symptomatic treatment alone was available, were cured by the eradication of the bacterium.[1] The last decade has seen the standardization of the treatment regimens for *H. pylori* eradication, and all of the consensus conferences world-wide have recommended the use of triple therapy consisting of a proton pump inhibitor (double dose) and two antibiotics, mainly clarithromycin (500 mg b.d.) and amoxicillin (1 g b.d.).[2–7] This treatment has been shown to be effective and safe in numerous clinical trials but, as expected, when applied to the whole population, the rate of success is reduced. The question of second-line therapy has been considered in the Maastricht 2-2000 Consensus Report, which recommends quadruple therapy.[7] Many other options have been used with various success rates. Nonetheless, doctors who treat this infection are always faced with a small number of patients for whom two or more treatment attempts have failed. These cases can be considered as refractory *H. pylori* infection.

In this article, we consider the following questions: when is it necessary to pursue the goal of eradication?; why does eradication treatment fail?; and what are the possible alternatives for the treatment of refractory *H. pylori* infection?.

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WHEN IS IT NECESSARY TO PURSUE THE GOAL OF ERADICATION?

For any treatment, the benefit obtained must be offset against the possible harm incurred. Millions of

individuals are infected by *H. pylori* world-wide, but the sole desire to eliminate a potentially deleterious bacterium is not a sufficient reason for therapy. If a patient suffers from non-ulcer dyspepsia, a disease which is only marginally linked to *H. pylori*, the immediate benefit of eradication treatment is limited.[8] However, if peptic ulcer is present, more than one eradication attempt should be considered.

More importantly, there are some life-threatening situations in which eradication must always be attempted. These include bleeding ulcers[9, 10] and gastric mucosa-associated lymphoid tissue lymphoma.[11–13] Several studies have shown the importance of *H. pylori* eradication in these situations. Mucosa-associated lymphoid tissue lymphoma can even be cured, except when genetic abnormalities, such as translocation t(11;18), are present.[14] In these diseases, the benefit of eradication largely overcomes any difficulties encountered in the process.

WHY DOES ERADICATION TREATMENT FAIL?

The essential reason for unsuccessful eradication is the lack of a sufficient concentration of antibiotics at the site of infection over a sufficient time period to overcome the minimal bactericidal concentration (MBC) of the bacterium, and therefore to eliminate it. Possible reasons for this are indicated in Table 1 and reviewed below.

Lack of patient compliance

Most patients are used to taking simple treatments, such as antisecretory drugs given once daily, rather than to taking three different drugs, which act synergistically, twice daily to cure one disease. Furthermore, the effect of triple therapy on symptoms may not be immediately obvious and, indeed, adverse events are quite frequent. Most clinical trials have reported an adverse event rate of approximately 30% which can make a patient's life very uncomfortable.[15] Diarrhoea is the most common symptom, and a bad taste in the mouth is frequently reported, amongst others. Therefore, in addition to the treatment's complexity, the occurrence of adverse events is often a reason for non-compliance.

Table 1. Possible reasons for the failure of *Helicobacter pylori* eradication therapy

Antibiotic concentration is low or zero because of a lack of patient compliance
Antibiotic concentration is lower than the minimal bactericidal concentration of the bacterium because of resistance acquired by mutations
Antibiotic efficacy is limited because the gastric pH is too low
Antibiotic concentration is not sufficient because of a high bacterial load
Other hypothetical reasons:
Existence of sanctuaries to which antibiotics do not diffuse
Existence of viable bacteria in dormant forms not accessible to antibiotics
Impaired host mucosal immunity
Re-infection

Clinical trials rarely report a lack of compliance as a cause of failure. However, this factor may be underestimated due to inadequate measurement. In a recent study carried out in Switzerland, using the Medication Event Monitoring System, i.e. a computerized compliance monitor which registers whether or not a drug container has been opened, 11.5% of patients stopped their treatment prematurely, two-thirds as a result of adverse events. Poor compliance was inversely associated with *H. pylori* eradication.[16]

It is possible that, in the 7-day regimen, which is currently recommended as the minimum length of treatment, the failure to take a few doses of drug may lead to a lack of eradication. It is the doctor's responsibility to explain to the patient that adverse events may occur, but that they are mild and do not necessitate stopping treatment. Often because of a lack of time, the recommendations are not given in an appropriate manner. Some physicians have spoken of 'resistant patients', but these individuals could be made to comprehend if given adequate explanation prior to treatment administration.

Selection of resistant mutants

H. pylori can become resistant to most antibiotics by chromosome mutation.[17] This is the essential resistance mechanism found in this bacterial species, although genetic exchanges, especially transformation, have also been documented.

Mutations occur spontaneously during replication,[18] with the possible exception of antibiotics acting on the DNA, like metronidazole, which itself can induce mutations. The administration of the antibiotic will select the resistant mutants. The mutations are primarily related to the antibiotic target which can no longer bind the antibiotic.

The most important resistance to consider is that of macrolides, especially clarithromycin. A point mutation occurring in one of two specific positions on the 23S rDNA is responsible for an important decrease in antibiotic binding to the ribosome and, consequently, the macrolide cannot interfere with protein synthesis.[19]

Targets for other antibiotics are given in Table 2. In all cases, point mutations lead to an increase in the minimal inhibitory concentration (MIC) and MBC, which are higher than the antibiotic concentrations achievable in the gastric mucosa.

Low gastric pH

The MBCs and MICs of most antibiotics against *H. pylori* are dependent on the pH of the environment. MICs are usually taken as surrogates of MBCs and are determined at pH 7 or pH 7.4. Indeed, at lower pH, the MIC increases. However, the loss of activity may vary according to the drug used (Table 3), and the standard method of MIC determination cannot be performed at pH < 5.

Table 2. Genes affected by point mutations or other genetic events leading to antibiotic resistance in *Helicobacter pylori* and the frequency of resistance

Antibiotic group	Genes affected	Frequency of resistance
Macrolides	23S rRNA	0–20%
Metronidazole	*rdxA*, *frxA*	10–90%
Quinolones	*gyrA*	0–10%
Rifamycins	*rpoB*	0–5%
Amoxicillin	PBP-1A	Few cases described
Tetracycline	16S rRNA	Few cases described

Table 3. Minimal inhibitory concentration (MIC) of various antibiotics against susceptible *Helicobacter pylori* according to pH (adapted from Goodwin and McNulty[20] and Mégraud[21])

	MIC_{90} (mg/L)		
Agent	pH 7.5	pH 6.0	pH 5.5
Penicillin	0.03	0.5	0.5
Ampicillin	0.06	0.25	0.5
Cefalexin	2	16	32
Erythromycin	0.06	2	8
Clarithromycin	0.03	0.06	0.25
Ciprofloxacin	0.12	0.5	2
Tetracycline	0.12	0.25	0.5
Nitrofurantoin	1	2	2
Metronidazole	2	2	2
Bismuth subcitrate	16	8	—

A unique characteristic of the ecological niche of *H. pylori*, the stomach, is acidity. An important component of triple therapy is therefore the antisecretory drug, which increases the pH of the stomach, thus allowing better antimicrobial activity.[22] This is why proton pump inhibitors are used and a double dose recommended. However, there are differences in gastric pH between individuals, and a small proportion of patients may be acid hypersecretors. The concept of acid hypersecretors, who are different from gastrinoma patients, was proposed by Hirschowitz. These subjects have a basal acid output of > 15 mmol/h but a normal gastrin level.[23] In these few patients, who possibly have a large parietal cell mass, the pH remains low and the antimicrobial activity may be insufficient to eradicate the bacterium. This cause of failure was identified to be of major importance when dual therapies, with amoxicillin as the only antibiotic, were used. Patients who failed eradication had low pH values during the night and after meals.[24] In addition, the negative impact of smoking on *H. pylori* eradication is also probably related to an increase in gastric acidity.[24]

Another possible cause of failure is the variation in proton pump inhibitor metabolism between patients. Proton pump inhibitors are, to a large extent, metabolized in the liver by cytochrome P450 isozyme CYP2C19. A polymorphism of the corresponding gene allows subjects to be classified as homozygous extensive metabolizers, heterozygous extensive metabolizers and poor metabolizers. Homozygous extensive metabolization may have a negative effect on *H. pylori* eradication. In a study with lansoprazole (30 mg), the mean 24-h intragastric pH value was pH 4.5 in homozygous extensive metabolizers vs. pH 5.5 in those who were poor metabolizers.[25] In another study, it was necessary to use a dose of omeprazole four times higher than normal to obtain the same area under the plasma concentration–time curve in extensive metabolizers vs. poor metabolizers.[26] However, clinical trials in which the polymorphism of CYP2C19 was taken into account did not show any significant difference in eradication rates.[27, 28]

It is possible that these trials were not sufficiently powered and, furthermore, they did not take other risk factors for failure into account in a multivariate analysis. When antibiotic resistance was also considered, the CYP2C19 genotype was not a risk factor for

failure.[29] Most of these studies were performed in Japan, and the proportion of extensive metabolizers in Caucasians remains to be determined.

High bacterial load

When determining the MICs of antibiotics *in vitro*, it is well known that the bacterial load can influence the result, especially for certain antibiotics.

There is no true quantitative test available for *H. pylori*, but some tests, such as histology and the urea breath test, can be considered to be semi-quantitative.[30] Several large studies (> 100 patients) have confirmed the role of a high bacterial load as a risk factor for treatment failure for both standard bismuth-based triple therapy[31, 32] and 1-week proton pump inhibitor-based triple therapy,[33, 34] and this was independent of the diagnostic method used, i.e. histology or urea breath test. Delta over baseline values greater than 35‰ definitely point to a high risk of failure using the urea breath test.

Topical agents, such as bismuth salts, may exert their beneficial effect by decreasing the bacterial load. This hypothesis is supported by the fact that focal accumulation of bismuth particles occurs under the cell wall of *H. pylori*, affecting most organisms after a few hours, and a bactericidal effect is detected in parallel.[35]

The surprising beneficial effect of alcohol on *H. pylori* treatment may relate to the lower bacterial load in alcohol consumers.[36]

Sanctuaries not accessible to antibiotics

The occurrence of intracellular *H. pylori* was first documented in 1990, when Wyle *et al*. observed intact and degenerated bacteria in epithelial, parietal and chief cells of patients.[37] This phenomenon is considered to be rare.[38] However, it is interesting to note that bacterial heat shock protein 60 can be expressed on epithelial cells, and this correlates with inflammation after eradication.[39]

In vitro, *H. pylori* is not killed efficiently by polymorphs.[40, 41] All strains are capable of invading Hep2 cells and other epithelial cells by receptor-mediated endocytosis.[42, 43] New techniques have recently been applied.[44, 45] Interestingly, studies have shown that intra-vacuolar *H. pylori* has a half-life of approximately 24 h and is able to repopulate the extracellular environment. The exploration of an intra-vacuolar niche is a new aspect of the biological life cycle of *H. pylori* which could explain the difficulties encountered in eradicating the bacterium. This is especially true when dual therapies with amoxicillin are used, as amoxicillin does not penetrate into the cells.[46] In contrast, when clarithromycin is used, a high intracellular concentration is achieved, and therefore this mechanism is less likely to occur.

It is also of interest to note that the effect of eradication treatment may not be the same throughout the stomach. When dual therapies are used, it has been shown that *H. pylori* may escape killing in the fundus.[47] More recently, Veldhuyzen van Zanten *et al*. have identified the transitional zone between antral and body regions as a potential site for sanctuary, as the pH gradient generated there may give an optimal environment for *H. pylori* growth.[48]

Dormant forms of H. pylori

This explanation refers to a very controversial area, i.e. the existence of viable but non-culturable forms of bacteria, which have been proposed for many different species, e.g. *Vibrio cholerae, Salmonella* sp. and *Campylobacter* sp.

Antibiotics require replicating bacteria to be active, and so if the bacterium is in a dormant form (viable but non-culturable), it will not be affected by antibiotics.

Coccoidal forms, which correspond to an evolution of the spiral form of *H. pylori*, are sometimes observed on smears prepared from biopsy specimens, whilst the culture remains negative. Such forms obtained from ageing cultures have been able to infect mice in some experiments.[49]

However, the genome sequence of *H. pylori* does not support the bacterium's adaptation to different life conditions, and a meticulous study of coccoidal forms has shown that coccoidal transformation is paralleled by a loss and degradation of DNA and RNA, as well as a loss of the membrane potential.[50]

Impairment of host mucosal immunity

Generally speaking, the immune system must function effectively in order to achieve the successful eradication of any pathogenic micro-organism.

In the context of *H. pylori* infection, therapeutic vaccination shows an effect by decreasing the bacterial load, and this has been related to the switch from a

T-helper-1 (Th_1) to a T-helper-2 (Th_2) immune response.[51] Borody *et al.* explored the link between *H. pylori* eradication using proton pump inhibitor triple therapies and blood T-lymphocyte production of interleukin-4, taken as a surrogate measure of mucosal Th_2 responses, and found a significant reduction of interleukin-4 in resistant patients compared with others.[52]

This interesting study, however, is jeopardized by the fact that most of the *H. pylori* strains in the failure group were resistant to clarithromycin and the group received this antibiotic. Indeed, the higher levels of interleukin-4 may be a consequence rather than a cause of the reduction in the bacterial load.[53] More studies are needed in this domain.

Early re-infection

An apparent failure in eradication may be due to early re-infection occurring during the 4 weeks or more between the end of treatment and the evaluation of its success.

Although this is theoretically possible, the probability appears to be very low and very difficult to prove. All epidemiological studies have shown that the risk of acquiring the infection is very low, except in childhood or when professional activities involve an exposure to gastric juice.[54]

To demonstrate a re-infection, the only tool available is molecular methods, which can show the non-identical nature of the isolates before and after treatment. If a re-infection occurs with the same strain, it is impossible to differentiate it from a recurrence of the same infection.

WHAT ARE THE POSSIBLE ALTERNATIVES FOR THE TREATMENT OF REFRACTORY *H. PYLORI* INFECTION?

Basic considerations

The aim is to use antibiotics to which *H. pylori* is unlikely to be resistant, to obtain a sufficiently high gastric pH and to ensure that the patient takes the drugs over a sufficiently long time period.

Choice of antibiotics. Clarithromycin is the most effective antibiotic against *H. pylori,* but the high rate of resistance which occurs in the case of failure of first-line therapy excludes the possibility of using this drug for further attempts, unless the MIC of the strain can be determined and the strain is susceptible. Indeed, in more than 60% of cases, a resistant mutant is selected.[55]

The preferred antibiotics are those for which resistance rarely occurs, i.e. amoxicillin or tetracycline, but these two antibiotics administered together lead to poor results.[56]

The problem of metronidazole is somewhat different. Resistance to metronidazole is very common in most *H. pylori* strains, but its impact on the clinical outcome is relatively modest. When strains are resistant, the rate of success with proton pump inhibitor-based triple therapies is 20% lower than that observed with susceptible strains,[57, 58] and even less with quadruple therapy.[59] Taking into account the excellent diffusion of metronidazole through the gastric mucosa,[60] and the partition hypothesis,[61] it is possible to overcome this resistance by increasing the duration of treatment.

There are also some antibiotics of interest which are more difficult to obtain, such as rifabutin[62] and furazolidone.[63] Resistance to rifabutin is rare, given that this group of antibiotics has only limited usage, and resistance to furazolidone is virtually absent.

The use of fluoroquinolones is controversial. Ciprofloxacin, despite its satisfactory *in vitro* activity against *H. pylori*, is not effective *in vivo*.[64] There are some claims that moxifloxacin, a new fluoroquinolone, gives better results than ciprofloxacin despite a comparable *in vitro* activity.[65] The same is true for levofloxacin. These results warrant confirmation. Furthermore, *H. pylori* resistance to quinolones is easily acquired and, in countries with a high consumption of these drugs, as in Portugal, the rate is already 9.6%.[66]

Increase in proton pump inhibitor dosage. As discussed above, some antibiotics show pH-dependent activity. This is not the case for tetracycline and metronidazole, which are components of the most commonly used quadruple therapy, but is the case for amoxicillin, which can be used in rescue triple therapies. For the latter therapies, it may be worthwhile doubling or tripling the dose of proton pump inhibitor to achieve a pH which is as close as possible to neutral.

Increase in the duration of treatment. In the first Maastricht Consensus Report, a 7-day treatment was proposed based on the results of numerous clinical trials.[2] This is probably the shortest acceptable duration and does not allow for any lack of compliance. For this

reason, the second Maastricht Consensus Report (2000) recommended at least a 7-day treatment.[7] In the case of refractory *H. pylori* infection, a 14-day treatment must be the rule, except with quadruple therapy.

Addition of a topical agent. Bismuth salts can be considered as topical agents as their absorption is limited and their efficacy is not related to absorption;[67] they operate most probably by destroying the bacteria in the manner of an antiseptic, rather than by inhibiting their growth in the manner of an antibiotic. Bismuth salts are usually included in rescue therapies. It is possible that they act by decreasing the bacterial load,[68] but, for practical reasons, they are administered at the same time as antibiotics.

Different salts are used: colloidal bismuth citrate, bismuth-subsalicylate and even a combination of bismuth salts with ranitidine (ranitidine bismuth citrate).

Adjuvant therapy: addition of probiotics. Probiotics may help to improve the success of *H. pylori* eradication in two ways: directly by lowering the bacterial load, and indirectly by decreasing the adverse events due to antibiotics and therefore improving compliance.

Probiotics may contribute to the decrease in bacterial load by inhibiting adherence and producing metabolites, bacteriocins or antibiotics which inhibit *H. pylori*. *Lactobacillus gasseri* (LG21), ingested in yogurt (10^7 colony-forming units/g) twice daily for 18 weeks, produced a decrease in urea breath test delta values.[69] A favourable effect of an acidified milk (LC1) was also observed on *H. pylori* gastritis in another study.[70] A culture supernatant of *Lactobacillus acidophilus* may also be beneficial to eradication.[71, 72]

Probiotics may also decrease the side-effects of antibiotics, especially diarrhoea, and increase compliance, as shown by Cremonini *et al.* using *Lactobacillus* GG, *Saccharomyces boulardii* or a combination of *Lactobacillus* and *Bifidobacterium*.[73, 74]

The other more usual approach to improve compliance is counselling and follow-up, which has been found to be successful.[75]

Recommendations

Empirical approach. The most widely used rescue therapy is quadruple therapy. It has the advantage of including tetracycline, an antibiotic for which resistance is not yet a problem, and metronidazole, an antibiotic for which resistance can be overcome. It includes bismuth salts, which have a synergistic effect on antibiotics, possibly by decreasing the bacterial load, and a proton pump inhibitor, which facilitates antibiotic activity by increasing the gastric pH.

Numerous studies have established the value of quadruple therapy as second-line therapy.[76] The complexity of this treatment has been partly solved by the recent availability of a special package.[77] In the case of failure, resistance to metronidazole may be suspected, and it can be replaced successfully by furazolidone.[78, 79]

However, there are countries in which bismuth salts are not available because of their toxicity. During the determination of the value of alternative proton pump inhibitor-based triple therapies, a large trial conducted in France confirmed that clarithromycin should be banned from second-line therapies and showed the potential of proton pump inhibitor–amoxicillin–metronidazole therapy given for 14 days.[80] Other proton pump inhibitor-based triple therapies which have been used successfully include proton pump inhibitor–tetracycline–metronidazole[81] and proton pump inhibitor–amoxicillin–rifabutin given for more than 7 days.[62, 82] Ranitidine bismuth citrate can easily replace the proton pump inhibitor (Table 4). These triple therapies, when compared with quadruple therapies, have the advantage of generating less adverse events. When a high level of metronidazole resistance is suspected, it can be replaced by furazolidone.[83, 84]

Exploration. The essential exploration to perform in the case of refractory *H. pylori* infection is antimicrobial susceptibility testing.

An endoscopy must be performed in order to culture the bacterium; the culture may take more than a week, but susceptibility testing is worthwhile. The main information obtained relates to clarithromycin. In the case of susceptibility to this drug, which still occurs in about one-third of cases after failure of first-line therapy

Table 4. Recommended regimens for refractory *Helicobacter pylori* infection when no susceptibility data are available

Drugs	Treatment duration
PPI, bismuth salts, tetracycline, metronidazole or	7 days
PPI (or RBC), amoxicillin, metronidazole or	14 days
PPI (or RBC), tetracycline, metronidazole or	14 days
PPI (or RBC), amoxicillin, rifabutin	10 days

PPI, proton pump inhibitor; RBC, ranitidine bismuth citrate.

including this drug, it should still be used because it has the best potential for eradication.[80]

In the event of a high level of metronidazole resistance, which may jeopardize the antibiotic's activity, furazolidone should be considered as an alternative. Susceptibility to tetracycline, rifamycins and amoxicillin is also usually confirmed. However, the strain may be resistant to all of the antibiotics commonly used, i.e. clarithromycin, metronidazole, tetracycline and rifamycins, and, furthermore, furazolidone and bismuth salts may not be available. In such difficult situations, if it is mandatory to eradicate the bacterium, dual therapy with proton pump inhibitor and amoxicillin can be prescribed.[85] Care must be taken to prescribe high doses of omeprazole (40 mg t.d.s.) and amoxicillin (1 g t.d.s.).[86, 87]

We do not recommend regimens including more than two antibiotics.

Other explorations have limited practical impact but can help to determine the problem. For example, a 24-h gastric pH measurement may be performed. As reported earlier, the same dose of proton pump inhibitor does not lead to the same acid inhibition in all patients. It depends on the parietal cell mass, which varies between individuals and also between different ethnic groups. Asians are known to have less gastric acidity than Caucasians, for example. It is possible to explore the CYP2C19 genotype using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) in order to determine whether or not the patient is an extensive metabolizer of the proton pump inhibitor. The results of these tests may lead to an increase in the proton pump inhibitor dosage in order to achieve an optimal pH.

Stomach mapping may be useful. It is not common to obtain biopsies from all parts of the stomach to look for *H. pylori*, but it may be interesting to have a picture of where the bacteria are located in the stomach. The persistence of bacteria may be determined by the local pH, and therefore this is an indirect exploration of gastric acidity.

Counselling. All patients with refractory *H. pylori* infection should receive counselling (Table 5).

Table 5. Counselling

No smoking
No alcohol (if metronidazole)
Describe adverse events
Propose follow-up

A risk factor for treatment failure in many trials is smoking, and consequently smoking must be strongly discouraged.

Alcohol must also be stopped, not because it is a risk factor for treatment failure, but due to its antagonistic effect with metronidazole, a compound included in most rescue therapies.

Physicians must also take the time to explain the particularities of this treatment, in particular that it is mandatory to take the drugs together and not sequentially, and that adverse events may occur and should not lead to the cessation of treatment when they are minor. Furthermore, a follow-up must be performed during treatment and soon after treatment.

CONCLUSIONS

Refractory *H. pylori* infection is a frustrating problem for physicians, given that early clinical trials gave such optimistic results in terms of eradication. An analysis of the different steps influencing successful eradication may provide clues to the problem. We now have concordant data indicating that the high bacterial load and high acid production in some patients may jeopardize treatment success, but the essential factor is the susceptibility of *H. pylori* to antibiotics, especially to clarithromycin. Some studies in which *H. pylori* susceptibility to antibiotics was determined before the first course of treatment reported a success rate of more than 95%.[88, 89] This indicates the way in which we should proceed in the future, especially as a tool for the detection of *H. pylori* and its resistance to clarithromycin directly on a gastric biopsy in less than 2 h is now available.[90] This preventive approach is recommended to avoid an increase in refractory *H. pylori* infection in the future. In addition, we emphasize the role of counselling to avoid a lack of patient compliance due to the adverse events of treatment. Another approach which would solve the problem is the development of a vaccine. In addition to the usual preventive function of a vaccine, an anti-*H. pylori* vaccine could also have a therapeutic facet. A therapeutic vaccine would circumvent the problem of antibiotic resistance and the risk of re-infection. However, despite intensive research in this domain, there is much that has yet to be achieved, and many years of antibiotic treatment for *H. pylori* eradication are foreseen.

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