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TOPIC HIGHLIGHT

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Culture-guided treatment approach for *Helicobacter pylori* infection: Review of the literature

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Abstract

The progressive loss of efficacy of standard eradication therapies has made the treatment of *Helicobacter pylori* (*H. pylori*) more challenging than ever. Endoscopic-guided antibiotic susceptibility testing had previously been suggested to guide treatment after failure of second-line therapies. However, its role has expanded over the years, in accordance with the current Maastricht Guidelines. Several authors have dealt with this topic, developing both efficacy trials and cost-effectiveness trials against resistant *H. pylori* infections as well as infections in naïve patients. However, results are not homogeneous enough to provide definite advice, because antibiotic resistance is not the only reason for treatment failure. Moreover, the culture-guided approach is surrounded by many practical issues, such as the availability of both endoscopy units and microbiology laboratories, and the need for a standard of quality that cannot be satisfied everywhere. Finally, pre-treatment susceptibility testing should be part - and not the only weapon - of a targeted, personalized strategy to overcome *H. pylori* infection.

Key words: *Helicobacter pylori*; Antibiotic resistance; Antibiotic susceptibility testing; Culture-guided approach; Personalized therapy

Core tip: Eradication of *Helicobacter pylori* (*H. pylori*) has become hard to achieve, mainly because of the decrease of standard therapies and the rise of antibiotic resistance. The role of antibiotic susceptibility testing in the management of *H. pylori* infection is therefore becoming greater than in the past. This paper provides an overview of data in the literature about the culture-guided approach against *H. pylori* infection.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is probably the most common human pathogen, affecting at least 50% of the population worldwide[1]. It plays a relevant role in the pathogenesis of chronic gastritis, peptic ulcer disease, gastric neo-

plasms [gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach], and is also associated with many extra-digestive diseases (such as idiopathic thrombocytopenic purpura or iron deficiency anemia)[2]. *H. pylori* was classified by the International Agency for the Research on Cancer (which forms a part of the World Health Organization) as a class I human carcinogen[3]. Because of these reasons, *H. pylori* eradication represents a major clinical need. Unfortunately, fighting against *H. pylori* has turned out to be more and more challenging over the years, mainly because of the huge decrease of efficacy of standard eradication therapies.

The objective of the present paper is to review previous research evidence about the efficacy and safety of the culture-based treatment approach for *H. pylori* infection.

ANTIBIOTIC TREATMENT OF *H. PYLORI* INFECTION: THE CURRENT SCENARIO

In reality, standard triple therapy [a seven-day treatment consisting of clarithromycin, amoxicillin or metronidazole and proton-pump inhibitors (PPIs)], proposed at the beginning as first-line treatment for *H. pylori* infection, has partially lost its initial efficacy, with inadequate eradication rates in most areas[4]. According to the latest Maastricht Guidelines developed by the European Helicobacter Study Group, in regions of low clarithromycin resistance, clarithromycin-containing therapies or bismuth-containing (bismuth salts, PPIs, tetracycline and metronidazole) quadruple therapy are recommended for first-line empirical treatment. Better results in first-line treatment can be achieved in several manners: increasing the dose of PPIs, prolonging the length of therapy, adding an adjuvant treatment (such as certain probiotics or prebiotics)[5], or changing amoxicillin to metronidazole as the second antibiotic. In regions of high clarithromycin resistance, the bismuth-containing quadruple therapy has been proposed as first-line treatment. In case of unavailability of this therapy, non-bismuth (three antibiotics plus PPIs) quadruple therapy and the so-called "sequential therapy" (that includes five days of PPIs plus amoxicillin followed by five more days of PPIs plus tinidazole and clarithromycin)[5] have been recommended as an alternative. Levofloxacin-based triple therapy or bismuth-containing quadruple therapy have been recommended as second-line treatment[5]. Finally, although many empirical rescue therapies have been attempted after failure of second-line treatment[6], both current and previously published Maastricht Guidelines[3,5] suggest antibiotic susceptibility testing to guide further therapies in this case, when possible.

ROLE OF ANTIBIOTIC SUSCEPTIBILITY TESTING IN THE ERA OF BACTERIAL RESISTANCE ISSUE

Failure of antibiotic treatment has become a real issue for physicians, because of several factors that can be respectively grouped into microorganism-related factors, host-related factors, treatment-related factors. *H. pylori* antibiotic resistance is widely recognized as the main reason for treatment failure[6].

Since amoxicillin resistance is rare worldwide (< 1%) and bacterial resistance to metronidazole does not significantly affect eradication rates[6], the main concern is about clarithromycin.

Prevalence of primary clarithromycin resistance is increasing worldwide. It markedly reduces *H. pylori* eradication rates following standard therapies. Three main rRNA-point mutations (A2143G, A2142G, A2142C of domain V) are responsible for more than 90% of clarithromycin resistance cases, and different prevalence rates of such mutations have been reported worldwide. These point mutations have been associated with both different levels of resistance and variable eradication rates. A2143G is associated with a higher eradication rate; it is also the most common point of mutation in the Italian population[7].

Prevalence of primary clarithromycin resistance has been extensively studied during the last years, and data are currently available from almost all areas in the world: it ranges from that seen in low-prevalence areas (< 15%-20%, according to Maastricht Guidelines) of Northern Europe (< 10%), Senegal (1%), Canada (4%), South Korea (4.5%), United States (12%), Italy (9.9%, even if highly variable, ranging from 0% to 25%), Japan (13%), to that seen in high-prevalence areas (> 15%-20%) of Southern Europe (> 20%), Iran (17%) or Pakistan (> 20%)[6-12].

Primary resistance rate has been assessed not only for clarithromycin, but also for other antibiotics: according to a large multicenter analysis by Mégraud *et al*[8], *H. pylori* resistance rates were 14.1% for levofloxacin and 34.9% for metronidazole in a European adult population, and were significantly higher for clarithromycin and levofloxacin in Western/Central and Southern Europe (> 20%) than in Northern European countries (< 10%)[8].

Moreover, antibiotic resistance should be considered as a dynamic concept, since its prevalence can change not only among different countries, but also between two different periods in the same area, as proven by both Eastern[13,14] and Western reports[15,16].

Finally, antibiotic resistance has been shown to be associated with the number of failing eradication treatments: the greater the number of unsuccessful attempts, the higher the rate of antibiotic resistance. This is especially true for clarithromycin, metronidazole and levofloxacin[17]. Recently, Mégraud *et al*[8] confirmed this data: a significant association was found between outpatient use of quinolones and the rate of levofloxacin resistance ($P < 0.0013$) and between the use of long-acting macrolides and clarithromycin resistance ($P < 0.036$).

In this context, the role of antibiotic susceptibility testing has been enlarged and enhanced, in accordance with official guidelines.

The latest Maastricht Guidelines indeed suggest per-

forming cultures of gastric biopsies and antibiotic susceptibility testing, not only after the second treatment failure, but also before the administration of a first-line therapy containing clarithromycin, at least in areas of high clarithromycin resistance, and prior to prescribing a second-line treatment. If upper endoscopy is performed for other reasons, in all regions worldwide, authors consider this approach as possibly cost-effective, and sensible in areas of high clarithromycin resistance anyway[5]. Even if sound, this recommendation has reached only a grade D, which is an expert opinion. However, several authors have faced the issue of antibiotic susceptibility testing, developing both efficacy trials and cost-effectiveness ones.

CULTURE-GUIDED APPROACHES FOR *H. PYLORI*

The efficacy of antibiotic susceptibility testing in driving the antimicrobial treatment for the eradication of *H. pylori* has been extensively investigated. Most authors have experience of a culture-based eradication strategy against resistant *H. pylori* infection, but some have applied it also in naïve patients.

Susceptibility of *H. pylori* to antimicrobial agents can be assessed by both invasive and non-invasive tests. Upper endoscopy with culture of gastric mucosal specimens and determination of mean inhibitory concentrations for each antibiotic is the most diffused test; nevertheless, this method is hampered by a relatively high rate of false negatives, showing a reported sensitivity that ranges from 70% to 90%[18].

Growth of *H. pylori* can be affected by many environmental factors, *e.g.*, the number of retrieved gastric specimens, the temperature and duration of the transport period, the features of the transport medium, the microaerophilic conditions and the selectivity of the culture media[19]; moreover, certain drugs such as antibiotics, bismuth salts, omeprazole and benzocaine influence *H. pylori* detection[20]. As recently shown[21], the sensitivity of culture is also greatly reduced by bleeding in patients with peptic ulcer.

Finally, antibiotic susceptibility testing is not available everywhere, and its cost may be hard to afford; in this regard, cost-effectiveness trials have been performed to assess the benefit of this perspective.

Recently, fecal tests have been developed to detect clarithromycin resistance of *H. pylori* in a non-invasive manner, with promising results[22,23].

Culture against resistant H. pylori

In the earliest Maastricht Consensus Conferences[24], the utilization of antibiotic susceptibility testing prior to antibiotic therapy had been suggested only after failure of the second-line treatment. In this regard, many studies were developed around the early years of the millennium, with mixed results.

Gasbarrini *et al*[25] showed the efficacy of a multi-step strategy for *H. pylori* in a large cohort (n = 2606) of patients. In this setting, 49 subjects were still infected after the second antibiotic course, and underwent upper endoscopy with *H. pylori* culture. They then received a third-line therapy consisting of a one-week quadruple bismuth-based scheme, established on *H. pylori* antibiotic sensitivity. *H. pylori* culture with antibiotic susceptibility testing was carried out in 39 out of 49 patients (80%), showing an overall high prevalence of multi-drug resistant *H. pylori* strains. In particular, macrolide resistance rates were higher for erithromycin (62%) and azithromycin (68%) than for clarithromycin (56%, which was the same for nitroimidazoles), while a low prevalence of tetracycline resistance (12%) and no resistance for amoxicillin were observed. The tailored quadruple therapy, based on the *in vitro* sensitivity of the tested antibiotics, achieved an eradication rate of 77% by per-protocol analysis and 52% by intention-to-treat analysis.

Some years later, Cammarota *et al*[26] treated 94 resistant patients with a culture-guided, third-line regimen (89 patients with a 1-wk quadruple regimen including omeprazole, bismuth, doxycycline and amoxicillin, and 5 patients with a 1-wk triple regimen containing omeprazole, amoxicillin and levofloxacin or clarithromycin) with excellent results: overall, 90% of patients eradicated *H. pylori*. The quadruple regimen was effective in 81 out of 89 subjects (92% by per-protocol analysis and 91% by intention-to-treat analysis) and the triple regimen in 4 out of 5 subjects (80%, both by per-protocol and intention-to-treat analysis). *H. pylori* strains were resistant to metronidazole in 100% of patients, in 95% to clarithromycin, in 31% to levofloxacin and in 5% to tetracycline; no resistance to amoxicillin was found in any patient. All subjects showed multiple (double or triple) resistance. Furthermore, primary resistance rates (considering drugs not included in any of the previously failed eradication regimens) were 86% for clarithromycin, 100% for metronidazole, 9% for levofloxacin.

These good results have not been reproduced in other studies. In two different trials from Spain[27,28], a two-week quadruple therapy driven by antibiotic susceptibility testing was administered as a third-line eradication attempt to patients with *H. pylori* resistant infection and peptic ulcer. Eradication rates ranged, respectively, from 36% to 52% in the first trial[27] and from 47.4% to 73.7% in the second one[28], depending on the given antibiotic regimen.

Only once was the role of antibiotic susceptibility testing evaluated in a selected setting of resistant subjects with at least four prior *H. pylori* eradication failures: in an open-label randomized controlled trial, Cammarota *et al*[29] assessed the efficacy of a pre-treatment with *N*-acetyl-cysteine (NAC) before a culture-guided antibiotic regimen in obtaining eradication. While in the NAC pre-treatment group *H. pylori* was eradicated in 65% (13 out of 20) of patients, only 20% (4 out of 20) of patients who were treated with a culture-based approach alone were successfully treated ($P < 0.01$).

A culture-based strategy has also been experienced as second-line therapy. Susceptibility-guided treatment was compared to empiric therapy in a setting of 98 patients suffering from *H. pylori* infection despite at least one treatment attempt, showing significantly higher eradication success (86%, 42 patients in guided-therapy group *vs* 63%, 31 patients in empiric-therapy group, $P = 0.02$)[30]. Fiorini *et al*[31] also achieved excellent results in a population of 236 consecutive *H. pylori*-positive subjects with a history of one or more treatment failures. Assessment of antibiotic susceptibility revealed a resistance rate of 44.5% for levofloxacin, 92.4% for clarithromycin and 72.9% for metronidazole, with high rates of multiple resistance. Patients received either a levofloxacin-based triple therapy or a rifabutine-based triple therapy, depending on their susceptibility to fluoroquinolones. Eradication rates ranged between 88.6% and 90%, depending on administered therapy.

Culture in first-line therapy

In order to overcome macrolide primary resistance, susceptibility testing-based regimens have also been attempted in naïve *H. pylori*-positive patients. In an open-label randomized controlled trial by Toracchio *et al*[32], 56 patients received a standard first-line triple therapy and 53 were treated according to the susceptibility test. Eradication rates in the standard group were, respectively, 81% and 75% by per-protocol and intention-to-treat analysis, while in the second group they were 98% and 91% ($P < 0.05$).

More recently, antimicrobial susceptibility testing was used in an open-label randomized trial by Molina-Infante *et al*[33] to treat naïve patients according to clarithromycin susceptibility or resistance. These authors compared tailored non-bismuth quadruple (concomitant) therapy to either standard triple therapy (in clarithromycin-susceptible *H. pylori* group) or sequential therapy (in clarithromycin-resistant *H. pylori* group). Tailored concomitant therapy was proven to be better than triple therapy and at least as effective as sequential strategy.

Cosme *et al*[34] showed that, in a population with high clarithromycin resistance, a first-line triple therapy (including omeprazole, clarithromycin and amoxicillin) achieves better eradication rates if patients are diagnosed by antimicrobial susceptibility testing rather than by C13 Urea Breath test (88% *vs* 49% eradication rate); this approach was also more cost-effective than standard empirical therapy (€571 *vs* €666 per patient).

Eastern reports have also shown interesting results, even with cutting-edge techniques. A pharmacogenomics-based personalized strategy, in which dosage of PPIs and selection of antibiotic regimen were assessed according to the respective patient *CYP2C19* and *H. pylori 23S rRNA* gene polymorphisms (using the serial invasive signal amplification reaction assay), was compared to the standard therapy in 300 *H. pylori*-positive patients. The tailored regimen group experienced significantly higher eradication rates than the control group both at the intention-to-treat (96% *vs* 70%, $P < 0.001$) and at the per-protocol analysis (97% *vs* 70%, $P < 0.001$). Furthermore, the mean cost for successful eradication of *H. pylori* per patient was cheaper in the tailored regimen group ($657) than in the standard regimen group ($669)[35].

Finally, a tailored non-invasive approach, based on the detection of clarithromycin resistance (through assessment of *H. pylori 23S rRNA* genotypes) in human fecal specimens, was attempted by Kawai *et al*[23] in a recent randomized controlled trial. The tailored group achieved significantly higher eradication rates than the control group (94.3% *vs* 71.4% at intention-to-treat analysis; 94.3% *vs* 78.2% at per-protocol analysis).

Is the culture-guided approach cost-effective?

A culture-based eradication strategy consists of several parts, each of which has a precise cost, such as endoscopic and biopsy procedures and materials, antibiotic susceptibility testing, administered drug regimens, workhours of physicians and other professionals. Over the years, few authors have tried to assess the cost-effectiveness of such approach.

In a cost-effectiveness study performed in 1999, Breuer and Graham[36] showed that an eradication strategy driven by antimicrobial susceptibility testing would be able to save $37 000 per 1000 patients treated in a US population.

Later, the culture-based eradication strategy showed cost-effectiveness in several trials, even as first-line treatment.

Romano *et al*[37] achieved savings of approximately $5 US per patient, in a setting of 150 treatment-naïve Italian patients.

As previously described, the culture-based approach was more cost-effective than standard first-line therapy in reports from Cosme *et al*[34] (€571 *vs* €666 per patient) and from Furuta *et al*[35] ($657 *vs* $669 per patient).

Cost-effectiveness can be defined as money saved per patient by using one particular approach over another, while achieving similar effectiveness (cure rates)[36]. Since *H. pylori* cure rates depend on several factors (*i.e.*, eradication regimen, behavior and compliance of patient, number of prior eradication therapies, geographical areas, and many others), obviously the cost-effectiveness of a strategy will also depend on them. Moreover, prospective savings of a strategy are strictly linked with the characteristics of the involved setting: performing pre-treatment susceptibility testing in patients with previous, independent indication to upper endoscopy or patients with peptic ulcer may be more or less economically suitable according to the target population.

Probably, the cost-effectiveness of the culture-based approach may change depending on these factors, and may be higher in some settings than in others. Nevertheless, available studies have involved wide populations without any stratification. Further cost-effectiveness trials, focused on targeted samples, or at least providing subgroup analyses, will probably clarify this issue.

Table 1 Summary of the available literature data

Line of tailored therapy	Ref.	Type of therapy	Patients (*n*)	Tailored therapy eradication rates per protocol/intention-to-treat analysis
First	Toracchio *et al*[32]	Triple	53	98%/91%
	Molina-Infante *et al*[33]	Quadruple	89	92%/91%
	Cosme *et al*[34]	Triple	117	88%/NR
	Furuta *et al*[35]	Triple	150	97%/96%
	Kawai *et al*[23]	Triple	35	94%/94%
Second	Yahav *et al*[30]	Triple	49	86%/63%
Third	Gasbarrini *et al*[25]	Quadruple	49	77%/52%
	Cammarota *et al*[26]	Quadruple	89	92%/91%
	Cammarota *et al*[26]	Triple	5	80%/80%
	Gomollón *et al*[27]	Quadruple	31	36%-52%/NR
	Vicente *et al*[28]	Quadruple	39	47%-74%/NR
Fourth	Fiorini *et al*[31]	Triple	236	89%-90%/NR

NR: Not reported.

CONCLUSION

Since *H. pylori* antibiotic resistance is rapidly growing worldwide, an eradication strategy based on pre-treatment susceptibility testing is going to get more interesting than in the past.

Culture of gastric specimens to assess antimicrobial susceptibility of *H. pylori* was initially applied as part of a rescue strategy against multi-resistant infections. As described above, such an approach achieved mixed results, probably related to the relatively high rate of false negatives. The procedure is indeed influenced by both host-related factors (bleeding, use of certain drugs)[32-34] and methodology-related factors (number of gastric biopsies, conditions of transport, laboratory characteristics)[35,36]. Moreover, *H. pylori* resistance of *H. pylori* strains often involves more than one antibiotic and the administration of the right therapy may be burdensome as a result. Empiric treatments including many antimicrobials, such as sequential regimens, could therefore be ineffective in cases of multiple resistance to antibiotics.

Resistant strains have shown higher susceptibility rates to amoxicillin, tetracycline and (to a lesser extent) levofloxacin, than to macrolides or nitroimidazoles. However, prior to choosing the optimal eradication regimen, several aspects should be considered, such as the number of former therapeutic failures[17,38], previous adverse reactions to a specific antibiotic, or the compliance of the patient. Moreover, the addition of non-antibiotic treatments, such as *N*-acetyl-cysteine[29], may be taken into account.

Over the years, the worldwide diffusion of primary clarithromycin resistance to *H. pylori* has become both a health and an economic burden. The culture-based strategy has therefore been experienced even in naïve patients, showing not only higher efficacy but also better cost-effectiveness than standard therapy. Such an approach would thus appear to be reasonable, for both the health of patients and economic reasons.

However, as of now, a culture-guided approach for the eradication of *H. pylori* cannot be applied everywhere, for several reasons. Endoscopy services are not available everywhere, and microbiology laboratories performing antibiotic susceptibility testing are even fewer. Furthermore, the whole process needs a standard of quality (in terms of both materials used for culture and skill of the microbiologist to grow *H. pylori*) that cannot be assured everywhere.

Another issue is that, as seen above, the real efficacy (in terms of eradication rate) of the culture-based approach can range widely, because antibiotic resistance is not the only reason for treatment failure. As an example, biofilm formation by *H. pylori* can lead to several unsuccessful eradication attempts regardless of genetic antimicrobial resistance, and targeted adjuvant therapies can improve the eradication rate of a culture-guided treatment[22]; further studies are needed in this regard. Moreover, since *CYP2C19* genotype polymorphisms influence serum concentrations of PPIs and their ability in inhibiting gastric acid secretion (and, consequently, the *H. pylori* eradication rates of PPI-based regimens)[39-44], the assessment of *CYP2C19* status and consequent modulation of PPI dosages may be part of a tailored therapy, as demonstrated by Furuta *et al*[35] with excellent results.

In conclusion, the few studies available so far have shown the feasibility of a culture-based approach for the eradication of *H. pylori* (Table 1). However, this should not be considered as the end of the line, but the forerunner of future large trials, specifically designed to assess the utility of antibiotic susceptibility testing as part of a personalized strategy to overcome *H. pylori* infection.

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