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Empirical or susceptibility-guided treatment for *Helicobacter pylori* infection? A comprehensive review

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***Abstract*:** Although susceptibility-guided therapy is frequently recommended for *Helicobacter pylori* infection, the evidence available to date supporting this strategy is limited. The aim of the present article is to review the advantages and limitations of the susceptibility-guided and the empirical strategies to treat this infection. We performed a bibliographic search to identify studies investigating *H. pylori* susceptibility-guided therapy. Culture is not the only way to assess antibiotic resistance, as different polymerase chain reaction-based approaches have been developed as alternative methods. For detecting *H. pylori* antimicrobial resistance, a molecular approach based on a stool sample might enable more convenient, time-saving methods. Unfortunately, the antimicrobial susceptibility cannot be obtained in all cases. Furthermore, antibiotic susceptibility testing in clinical practice yields useful information only for a few antibiotics: clarithromycin, metronidazole, and quinolones. In addition, susceptibility towards clarithromycin and metronidazole *in vitro* does not necessarily lead to eradication *in vivo*. In the case of *H. pylori* therapy failure, we should not re-administer any of the antibiotics against which *H. pylori* has probably become resistant. Our updated meta-analysis showed that susceptibility-guided treatment is not better than empirical treatment of *H. pylori* infection in first-line therapy if the most updated quadruple regimens are empirically prescribed, and similar efficacy results were also demonstrated with the two strategies for second-line therapy. Cumulative *H. pylori* eradication rate with several successive rescue therapies empirically prescribed reaches almost 100%. Finally, the studies that have evaluated the cost-effectiveness of the susceptibility-guided treatment have achieved contradictory results. In summary, we can conclude that the evidence is too limited to support the generalized use of susceptibility-guided therapy for *H. pylori* treatment in routine clinical practice, either as first-line or as rescue treatment. Nevertheless, it would be recommended that susceptibility tests are performed routinely, even before prescribing first-line treatment, in specialized centers with an interest in *H. pylori* management.

Keywords: culture, empirical, *Helicobacter pylori*, susceptibility, tailored

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Introduction

Helicobacter pylori (*H. pylori*) infection affects billions of people worldwide, being the main cause of gastritis, peptic ulcer disease, and gastric cancer.[1] Antibiotic resistance is the major factor affecting our ability to cure *H. pylori* infection, and the rate of resistance to several antibiotics, mainly clarithromycin, is steadily increasing in many geographic areas.[2–5] A recent systematic review and meta-analysis assessed the distribution of *H. pylori* resistance to commonly used antibiotics in 65 countries, and found that primary resistance rates to clarithromycin, metronidazole, and levofloxacin were ⩾15% in most regions. Furthermore, increasing antibiotic resistance was observed in most regions.[6] Accordingly,

the World Health Organization has designated clarithromycin-resistant *H. pylori* a high priority for antibiotic research and development.

As antibiotic resistance is an evolving process, it seems mandatory to carry out point-prevalence surveys on a regular basis.[3] A strategy that has been suggested to increase the eradication rate is to provide individualized (personalized) treatment according to antibiotic susceptibility testing. However, the true utility of performing antibiotic susceptibility testing and the moment when it must be performed (before the first treatment or only after eradication failure) are both controversial. Of note, *H. pylori* culture is time consuming, not always available on a routine basis, offering quite low sensitivity, and obviously implying the performance of an endoscopic exploration.[7,8] Furthermore, culture is relatively expensive, not because of the cost of the procedure *per se*, but mainly because of the costs of the associated endoscopy required to obtain biopsy specimens.

Although susceptibility-guided therapy has been recommended in many *H. pylori* consensus conferences,[9–11] the studies evaluating this strategy are, however, quite limited, and the evidence available to date about when and in whom culture should be performed is surprisingly scant. In fact, currently, most physicians treat *H. pylori* infection without relying on antimicrobial susceptibility testing to choose the best regimen.

The aim of the present article was to review the advantages and limitations of susceptibility-guided and empirical strategies to treat *H. pylori* infection.

Search strategy

Bibliographical searches were performed in the MEDLINE and EMBASE electronic database up to April 2020 based on the following words (all fields): pylori AND [(culture OR culture-based OR culture-guided OR tailored OR susceptibility OR susceptibility-guided OR "antimicrobial susceptibility" OR "susceptibility testing") OR (empiric OR empirical)]. Articles published in any language were included. Reference lists from the articles selected by electronic searching were examined in detail to further identify relevant studies. Abstracts of the articles selected in each of these multiple searches were reviewed, and those dealing with susceptibility-guided treatment of *H. pylori* infection were recorded. The number of articles identified with PubMed was 6355, and with EMBASE 9607; after excluding duplicates, 12,736 articles were finally identified and reviewed.

What are the main arguments for assessing the antibiotic susceptibility of *H. pylori*?

The proportion of patients who achieve *H. pylori* eradication depends mainly, on the prevalence of antimicrobial resistance in the particular population being treated. Therefore, if the proportion of resistant infections is unknown, the results in any population cannot be generalized to another population with a different proportion of antimicrobial resistance.[12] Empirical therapy that takes into consideration the local resistance patterns may be superior to predict the efficacy of any *H. pylori* eradication regimen. Therefore, the local resistance patterns and the efficacy rates in the context of a specific environment are essential for establishing a correct treatment of the infection in real-world settings.[13]

Furthermore, it has been suggested that it appears unjustified to prescribe an antibiotic that will lack efficacy, generate higher cost, and will induce adverse events. A disadvantage of empirical treatment is that it often contains three, partly unnecessary, antibiotics, implicating the misuse of antibiotics. Susceptibility testing has been proposed to reduce unnecessary antibiotic prescription.[14] For example, performing antimicrobial susceptibility testing before first-line therapy might still allow the administration of the standard clarithromycin-based triple therapy to patients with an *H. pylori* clarithromycin-susceptible strain in areas with high overall clarithromycin resistance.[15]

Another obvious benefit of this strategy is that through the application of susceptibility testing prior to treatment, the development of antimicrobial resistance can be minimized,[15] as antibiotic use in the outpatient community is positively correlated with antibiotic resistance.[3] Emergence of antibiotic resistance after widespread use of antibiotics is an important concern especially for mass screening and eradication of *H. pylori* in asymptomatic subjects in the community. Nevertheless, the transient increase of antibiotic resistance to certain bacteria observed immediately after

antibiotic treatment may be restored to basal state shortly (2 months) after *H. pylori* eradication treatment has been administered.[16] Finally, it has been reported that there is a significant short-term perturbation of gut microbiota after *H. pylori* eradication.[17,18] However, the diversity of gut microbiota may be fully restored several months or years after prescribing eradication therapy.[19,20]

Is culture the only way to assess antibiotic resistance to *H. pylori*?

In routine clinical practice, the detection of *H. pylori* antimicrobial resistance is mainly based on culture, including gradient diffusion susceptibility testing (E-test) and the agar dilution method.[15] These phenotypic assays offer the opportunity to determine the minimal inhibitory concentrations of the antibiotics. Antibiogram is the only available way to test the susceptibility to all antibiotics.

Recently, different polymerase chain reaction (PCR)-based approaches have been developed as alternative methods to culture. These techniques allow assessing point mutations responsible for antibiotic resistance.[21] PCR-based tests are, at present, available mainly for the detection of clarithromycin and levofloxacin resistance. A recent systematic review evaluated the feasibility of genotypic detection methods compared with phenotypic detection methods, and concluded that the genotypic detection methods were reliable for the diagnosis of clarithromycin and quinolone resistance in the strain and biopsy specimens; the A2142G/C and/or A2143G combination had the best sensitivity and specificity for the detection of clarithromycin resistance.[22] Although genotypic methods to evaluate antibiotic resistance were initially developed for macrolides, more recently they have also been evaluated for other antibiotics: the *rdxA* and *frxA* genes were found to contribute to metronidazole resistance, a relationship was found between 16S ribosomal DNA mutation and tetracycline resistance, and the role of the *gyrA* gene in fluoroquinolone-resistant strains was also determined.[22] However, the use of genotypic methods for the detection of metronidazole resistance is not yet established.

Molecular tests are faster than conventional culture-based assays. Culture is time consuming (it takes approximately 10 days to culture *H. pylori* and measure the minimal inhibitory concentration), especially when a low bacterial load is present, as generally occurs after eradication failure.[7] In this respect, PCR-based, culture-free techniques are accurate in genotypically finding even minimal traces of certain resistant strains. Finally, PCR is technically feasible for clinical application in small- and medium-sized hospitals in developing countries.[23]

The correlation between antimicrobial susceptibility testing performed by culture and antibiogram *versus* a molecular test, essentially real-time PCR, is not perfect. This relatively low concordance may be due to different factors: the relative low sensitivity of phenotypic investigation, the possibility that an E-test may identify resistant strains with point mutations different from those tested by PCR, or its inability to detect hetero-resistance (defined as the coexistence of strains susceptible and resistant to the same antibiotic in the same patient).[21,24] In this respect, molecular tests are able to detect more cases of hetero-resistance than culture, and an isolate could be mistakenly considered susceptible if a single biopsy is used for antimicrobial tests.[13,25]

Are gastric biopsies the only useful samples to study antibiotic susceptibility?

For detecting *H. pylori* antimicrobial resistance, a molecular approach based on a stool sample might enable more convenient, time-saving methods that facilitate the applicability of susceptibility-guided treatment. Some studies have shown an overall high sensitivity and specificity when comparing fecal DNA samples with culture or PCR on gastric biopsies to evaluate clarithromycin susceptibility.[21] However, noninvasive molecular tests are currently at a very early phase of development.[21] In fact, the aim of a recent meta-analysis was to provide pooled diagnostic accuracy measures for stool PCR test in the diagnosis of *H. pylori* infection.[26] Overall, 26 studies identified met the eligibility criteria, and it was found that stool PCR test had a performance of only 71% sensitivity (the main limitation of these stool tests seems to be the presence of PCR inhibitors of the feces that may cause false-negative results), although with a 96% specificity. The authors concluded that, in descending order of significance, the most diagnostic candidate genes using PCR detection were *23S rRNA, 16S rRNA, and glmM*, and that PCR for the *23S rRNA* gene, which has the highest performance, could be applicable to detect *H. pylori* infection.[26]

Susceptibility-based strategy and test-and-treat strategy: a contradiction?

Endoscopy has several obvious disadvantages: firstly, it is expensive and uncomfortable. In addition, it frequently involves prolonged waiting times. Furthermore, as the majority of endoscopy findings are normal they do not contribute to management. In summary, although performing an endoscopic evaluation of the upper gastrointestinal tract in all dyspeptic patients is a theoretical option, it is not realistic in clinical practice.

Several diagnostic strategies have been proposed for selecting patients with dyspeptic symptoms who are expected to benefit most from endoscopy. The ''test-and-treat'' strategy is based on the investigation of the presence of *H. pylori* and its subsequent eradication when detected. Several decision analyses and prospective studies support the use of the test-and-treat strategy for dyspeptic patients,[27,28] therefore it has been recommended by all international consensus conferences.[9–11] To avoid the theoretical risk of delaying the diagnosis of a malignant neoplasm, this strategy has been recommended only in young patients with no alarm symptoms; otherwise, endoscopy should be performed.

Taking into account that dyspepsia is the main indication for *H. pylori* eradication, it seems that a contradiction exists in recommending the application of a susceptibility-based strategy and the test-and-treat strategy, as culture obviously implies the performance of an endoscopic exploration to obtain biopsy specimens. However, this apparent contradiction could disappear in the near future if we had noninvasive methods to evaluate antibiotic susceptibility, for example from stool samples. Unfortunately, as previously discussed, stool molecular tests are currently at a very early phase of development.[21]

Finally, the feasibility of the susceptibility-based (endoscopic) strategy has not been properly evaluated. Most studies using susceptibility-guided therapy only include patients with a positive culture. Therefore, the number of susceptibility-guided therapy failures due to patients' refusal of endoscopy has not been estimated or included.[29] In fact, when the applicability and effectiveness of this strategy was reviewed,[29] the rate of acceptance of endoscopy for biopsy and culture was described only in one article with only 60 patients, and was reported to be as low as 60%.[30]

What is the success rate of culture to provide information about antimicrobial susceptibility?

Unfortunately, the antimicrobial susceptibility cannot be obtained in all cases (i.e. the sensitivity of bacterial culture is not 100%).[31] Even in the optimal conditions usually encountered in clinical trials, when both gastroenterologists and microbiologists are highly motivated, a culture sensitivity of no more than 90% is achieved in treatment-naïve patients. Furthermore, the bacterium was isolated in <80% of cases in several studies, including patients who had failed at least one eradication treatment.[7]

Growth of *H. pylori* can be affected by many environmental factors, such as the number of obtained gastric specimens, the duration and temperature of the transport period, the microaerophilic conditions and the selectivity of the culture medium.[32] Moreover, certain drugs such as bismuth salts, antibiotics and proton pump inhibitors (PPIs) may negatively influence *H. pylori* detection.[32] Therefore, in routine clinical practice an even lower (60–80%) probability of isolating the bacterium is to be expected.[7,29,32] Taking into account that a rate of acceptance of endoscopy of only 50–60% has been estimated, resistance would be finally determined in only approximately 50% of the patients to whom endoscopy and culture were offered.[29]

What useful information, from which antibiotics, can be obtained from culture?

The standard method (culture and antibiogram) is the only way to test the susceptibility to all antibiotics. However, antibiotic susceptibility testing in clinical practice yields useful information only for a few antibiotics. Antibiotics effective and generally used against *H. pylori* are mainly the following five: amoxicillin, clarithromycin, metronidazole, tetracycline and quinolones. Resistance to amoxicillin has been estimated to be as low as 0–1%; similarly, resistance to tetracycline has been reported to range from 0% to 5%. Hence, their role in clinical practice may even be marginalized. Finally, the relevance of *in vitro* metronidazole resistance for the *in vivo* treatment is quite limited (see next section). On the other hand, resistance to clarithromycin and quinolones is rapidly increasing and has reached alarming levels worldwide, and its clinical relevance is doubtless. Therefore, it may even be

assumed that antibiotic susceptibility testing in clinical practice yields useful information only regarding clarithromycin and quinolones.

What is the correlation between *in vitro* (culture) and *in vivo* (eradication rate) results?

On one hand, susceptibility towards clarithromycin and metronidazole *in vitro* does not necessarily lead to eradication *in vivo*. Thus, even knowing the susceptibility of *H. pylori*, eradication rates do not achieve 100%.[33,34] In this respect, retreatment of *H. pylori* using a therapy regimen including metronidazole achieves only a 70–90% eradication rate in those patients harboring metronidazole-susceptible strains. Likewise, only a 70–80% success rate is obtained in those patients infected with clarithromycin-sensitive strains when using a clarithromycin-based regimen.[7] A recent systematic review assessed infection cure rates in patients harboring strains found to be susceptible to the antibiotics administered in clinical trials in which the efficacy of second-line treatments was evaluated. This review reported a cure rate of only 72% in the patients harboring a clarithromycin-susceptible strain after previous clarithromycin treatment.[29] Therefore, the authors concluded that susceptibility-guided treatment alone did not achieve adequate cure rates for rescue therapies.[29]

On the other hand, the contrary is also possible: *H. pylori* eradication may be achieved in the presence of *H. pylori* metronidazole- or clarithromycin-resistant strains even with a drug combination including these antibiotics. This translates that *in vitro* resistance to either clarithromycin or metronidazole could sometimes be overcome *in vivo* by prescribing these antibiotics.[7] As an example, the European Registry on *H. pylori* Management (Hp-EuReg)[35] showed that the standard triple therapy with a PPI, clarithromycin and amoxicillin was effective in almost 80% of patients with clarithromycin resistance.[36] Furthermore, probably due to the synergistic effect of bismuth, the addition of this drug to a triple therapy with clarithromycin may allow achieving a cure rate of approximately 90% even in patients with resistance against this antibiotic.[37,38] Finally, it has been shown that vonoprazan, a novel gastric acid suppressant, is superior to conventional PPI-based therapy for the eradication of clarithromycin-resistant *H. pylori* strains.[39]

The lack of concordance between *in vitro* and *in vivo* results may be due to the fact that the *in vitro* test might not reflect the actual levels of active antibiotics in the gastric lumen, where pH may exert an influence on antimicrobial activity. In addition, some discrepancies between antibiotic susceptibility and *H. pylori* eradication may occur, due, for example, to the possibility of coinfection with different *H. pylori* strains.[13,40]

Should antibiotics be repeated, especially after *H. pylori* eradication failure?

When a regimen has to be selected to treat *H. pylori* infection, we have several data that will aid us in suspecting resistance to a particular antibiotic, without the necessity of a culture. In naïve patients, a suggested strategy is to choose the best regimen for a population according to the prevalence of antibiotic resistance. The effectiveness of a treatment for *H. pylori* can be predicted as long as its efficacy in resistant and susceptible strains and the prevalence of antibiotic resistance are known in the specific population.[41] For this to be possible, epidemiological surveys evaluating resistances in each country or region should be conducted on a regular basis. Moreover, it is very important to ask patients about previous exposure to antibiotics, particularly macrolides and fluoroquinolones, for any reason, as this provides a proxy for underlying antibiotic resistance to *H. pylori*.[3,42] Thus, in areas where *H. pylori* clarithromycin resistance is known to be low (<15%) and in patients with no previous history of macrolide exposure (for any reason), clarithromycin triple therapy may still be a valid first-line treatment option.[10]

Regarding rescue treatment, after failure of a first-line eradication regimen, the remaining *H. pylori* will show very high resistance to some (though not all) of the prescribed antibiotics.[43,44] Resistance to amoxicillin and tetracycline is extremely rare, even after failure of treatment including these antibiotics. The same applies to bismuth: no *in vitro* resistance to this drug has been described.[45] By contrast, after treatment failure, resistance to clarithromycin, quinolones and metronidazole reach virtually 100%. As the efficacy of clarithromycin- and quinolone-containing regimens is strongly affected by clarithromycin and quinolone resistance, repeating these drugs in rescue treatments is discouraged.[33,46,47] Even if resistance to these antibiotics does not appear, it remains uncertain whether

their re-administration is adequate, as they were not efficacious (for unknown reasons) for the first time. In fact, a major finding of a recent systematic review was that, even if the culture shows a clarithromycin-susceptible strain, repeating clarithromycin after a first treatment failure with this drug should be discouraged.[29]

With regard to metronidazole, some studies suggest that *in vitro* metronidazole resistance has a limited impact on the efficacy of *H. pylori* treatments when sufficiently long treatments and high metronidazole doses are used. However, a recent multicenter study showed that cure rates of a 14-day, high-dose, rescue triple metronidazole–amoxicillin–PPI therapy were as low as 37% in patients with previous metronidazole administration.[48] Therefore, it is suggested that repeating this antibiotic is only recommended when it is indispensable and in the setting of bismuth-based quadruple therapies.[37,49,50] In this respect, an advantage of prescribing a bismuth-based quadruple therapy is that we do not need to worry about previous antibiotic use as the risk of having a tetracycline resistant strain is extremely low and metronidazole resistance has limited impact on effectiveness of this regimen.

Regarding the optimal dose of the antibiotics, both in first-line but especially in rescue therapies, to obtain maximal pharmacodynamic effect, although amoxicillin is generally dosed twice daily, prescribing this antibiotic in more frequent doses (e.g. three or four times daily) has been suggested to improve efficacy.[37,38] On the other hand, the recommended metronidazole dosage for the majority of infectious diseases is 7.5 mg/kg three times a day with a plasma half-life of the molecule between 7 and 10 h. Several studies have shown good eradication rates using high doses and three-times-a-day schedules of both amoxicillin and metronidazole.[37,38] Regarding the optimal duration of *H. pylori* eradication treatment, it should be 14 days, unless a shorter scheme has been shown locally to be equally effective.[37,38] Finally, high-dose PPI therapy is recommended for triple therapy, and may probably increase the efficacy of a nonbismuth concomitant regimen as well. Nevertheless, more pharmacokinetic and pharmacodynamic studies are necessary to clarify these issues.

It has been suggested that endoscopy with culture may be appropriate after failure of two eradication therapies. For example, Cammarota *et al.* assessed the efficacy of a third-line, culture-guided treatment approach.[51] After the first two eradication attempts, 95% of patients were resistant to clarithromycin, and all were resistant to metronidazole. Consequently, most patients received a quadruple therapy consisting of PPI, bismuth, tetracycline and amoxicillin, and *H. pylori* eradication was achieved in 90% of the cases. The authors concluded that a third-line culture-guided therapeutic approach is effective; however, it would seem more appropriate to conclude instead that the bismuth-, tetracycline- and amoxicillin-based quadruple regimen would be an appropriate empirical third-line rescue treatment option (as it would not be necessary to know antibiotic susceptibilities to choose a regimen that simply implies not re-administering clarithromycin or metronidazole).

In summary, the position in the case of *H. pylori* therapy failure would be clear: not to re-administer any of the antibiotics against which *H. pylori* has probably become resistant. Although it may seem illogical, some studies have demonstrated that the repetition, even of exactly the same antibiotic regimen after *H. pylori* eradication failure, is not exceptional in clinical practice.[52,53]

As a representative example of this empirical strategy of not repeating key antibiotics, rifabutin-based rescue therapy constitutes an encouraging fourth-line strategy after multiple previous eradication failures with key antibiotics such as clarithromycin, metronidazole and levofloxacin.[54] The use of furazolidone, an antimicrobial drug that is active against a broad spectrum of bacteria and protozoa, may also be a good alternative for empirical treatment after several eradication failures.[55]

What is the comparative effectiveness of susceptibility-guided *versus* empirical strategy for first-line treatment?

The Maastricht V consensus report stated that "it is recommended to perform clarithromycin susceptibility testing when a standard clarithromycin-based treatment is considered as the first-line therapy, except in populations or regions with well documented low clarithromycin resistance (<15%)".[9] However, the scientific evidence supporting this statement is limited. Several meta-analyses have compared cure rates of susceptibility-guided *versus* empirical therapy for *H. pylori* first-line treatment.

The first meta-analysis was published by Wenzhen *et al.* in 2012 and was focused specifically on first-line treatment.[56] Only five randomized controlled trials (RCTs) were included, and it was concluded that culture-guided triple therapy was more effective than standard triple therapy for first-line treatment.

The second meta-analysis was published by Lopez-Gongora *et al*.[57] RCTs were selected and analyzed separately for first- and second-line treatments. In first-line treatment (nine studies), susceptibility-guided therapy was more efficacious than empirical 7–10 day triple therapy (which was the regimen prescribed in most studies).

The third meta-analysis was published by Chen *et al.* in 2016, and included both randomized and nonrandomized controlled clinical trials (nine studies in total).[58] First-line tailored therapy achieved higher eradication rates than empirical regimens.

We have just performed (in 2020) an updated meta-analysis comparing empirical *versus* susceptibility-guided treatment of *H. pylori*,[59] including 40 studies.[60–100] When only assessing first-line treatments, better efficacy results were obtained, overall, with the susceptibility-guided strategy (although the results were borderline statistically significant). However, when considering only empirical up-to-date first-line quadruple regimens (that is excluding the suboptimal triple therapies) no differences in efficacy were found *versus* the susceptibility-guided group. This lack of difference was confirmed when only RCTs were included and studies based on CYP2C19 gene polymorphism were excluded. Therefore, we concluded that susceptibility-guided treatment is not better than empirical treatment of *H. pylori* infection in first-line if the most updated quadruple regimens are empirically prescribed.

What is the comparative effectiveness of susceptibility-guided *versus* empirical strategy for second-line treatment?

Some meta-analyses have compared *H. pylori* cure rates of susceptibility-guided therapies *versus* those of empirical therapy specifically for second-line treatment. In the previously mentioned meta-analysis by Lopez-Gongora *et al*. only four RCTs that included *H. pylori* second-line rescue therapies were found.[57] Results were highly heterogeneous and no significant differences were found between susceptibility-guided and empirical strategies in terms of efficacy. The other meta-analysis previously mentioned, performed by Chen *et al.* also found no differences between tailored and empirical rescue regimens, although only three studies were included.[58] Finally, in the updated meta-analysis we have just performed, when including only second-line regimens, similar efficacy results were demonstrated with the two strategies (tailored and empirical) both when all the comparative studies were included and when only the RCTs were considered.[59]

What is the effectiveness of susceptibility-guided strategy for third-line treatment?

It has been frequently recommended that performing culture at first-line treatment or after a first eradication failure may not be necessary and therefore assessing *H. pylori* sensitivity to antibiotics in clinical practice may be suggested only after failure of the second treatment.[101] However, previous meta-analyses could not find any RCT comparing cure rates of susceptibility-guided therapies *versus* those of empirical third-line therapy.[57] In our updated meta-analysis, only two studies including at least third-line rescue regimens were identified, and similar efficacy results were found between both tailored and empirical strategies.[86,88]

The aim of a recent systematic review was to evaluate the effectiveness of susceptibility-guided therapy as third-line therapy (without comparing it with empirical treatment).[102] Four observational studies were included (no comparative studies were found), and the pooled mean eradication rate with susceptibility-guided therapy was only 72%. Therefore, the authors concluded that susceptibility-guided therapy may be an acceptable option as rescue treatment, but cure rates are, at best, moderate; therefore, the evidence in favor of susceptibility-guided therapy as rescue therapy is currently insufficient to recommend its use.[102]

Are the results from studies comparing empirical *versus* susceptibility-guided strategies reliable?

There are some relevant limitations affecting comparative studies, and consequently also the reliability of the meta-analyses including these studies, which are summarized as follows.

A major limitation of the current evidence regarding susceptibility-guided therapy is that comparative studies of susceptibility-guided therapy randomized patients after diagnostic endoscopy or even after successful culture has been performed.[57] Therefore, the comparative effectiveness of susceptibility-guided therapy *versus* the noninvasive diagnosis and empirical treatment strategy in patients where *H. pylori* infection is suspected (but not yet proven) has not been evaluated in randomized trials. Thus, a study adequately evaluating the effectiveness of susceptibility-guided therapy as a first-line treatment should randomize patients with uninvestigated dyspepsia into noninvasive testing *versus* endoscopy plus culture groups. In this same line, most of the studies evaluating the effectiveness of susceptibility-guided therapy as rescue therapy included the patients when culture had been already obtained. Therefore, the effectiveness of susceptibility-guided therapy (with endoscopy) and empirical rescue therapy (without endoscopy) has never been properly compared.[102] In this respect, the Maastricht V consensus report stated that "after a first failure, if an endoscopy is carried out, culture and standard antimicrobial susceptibility testing are recommended to tailor the treatment".[9]

A second limitation is that previous meta-analyses showed that susceptibility-guided therapy was more effective than empirical 7–10 day triple therapy, which was the standard treatment when most of the studies were conducted. However, clarithromycin-containing triple therapies are currently known to generally achieve poor cure rates and, therefore, are suboptimal comparators in most settings (mainly in regions with high clarithromycin resistance). However, there is limited evidence comparing this empirical approach with the highly effective bismuth or nonbismuth quadruple therapies currently recommended.[9] In fact, as previously noted in our updated meta-analysis, when only empirical first-line quadruple regimens were included, no differences in efficacy were found *versus* the susceptibility-guided group.[59] This results are in agreement with the well-known high effectiveness of bismuth quadruple therapy, even in patients with clarithromycin or metronidazole resistance; and also with the encouraging results of nonbismuth quadruple concomitant therapy, even when single clarithromycin or metronidazole resistance is present (only dual clarithromycin and metronidazole resistance seems to jeopardize effectiveness with this regimen).[103]

A final limitation is that many of the comparative studies evaluating susceptibility-guided *versus* empirical treatment included susceptibility testing for only one antibiotic (clarithromycin); metronidazole susceptibility was assessed in only some cases; and quinolone resistance was only exceptionally evaluated.

What is the cumulative *H. pylori* eradication rate with successive empirical treatments?

In designing a treatment strategy we should not focus on the results of primary therapy alone (although this should obviously be our primary goal); an adequate strategy for treating this infection should use several therapies which, if used consecutively, come as close to the 100% cure rate as possible.[101] In this sense, some studies have evaluated different empirical regimens after failure of two or more eradication treatments and have achieved a final (overall) eradication rate of almost 100%.[7,104–118]

In our previous experience, we aimed to evaluate the efficacy of different rescue therapies empirically prescribed during 10 years to 500 patients in whom at least one eradication regimen had failed.[104] Antibiotic susceptibility was unknown, and therefore rescue regimens were chosen empirically. Overall, *H. pylori* cure rates with the second-, third-, and fourth-line rescue regimens were 70%, 74%, and 76%, respectively. Thus, although the effectiveness of rescue regimens could not be considered ideal, cumulative *H. pylori* eradication rate with four successive treatments was 99.5%.

These results have been recently updated, including 1200 patients and 18 years of follow-up, and the cumulative effectiveness after five consecutive therapies was 99.8%, demonstrating that eradication can be achieved virtually in all cases by the administration of several consecutive empirical therapies, based just on the previously prescribed regimens.[119] Empirical strategy should be based on the avoidance of repeating similar eradicating schemes in the same patients during the course of different eradicating regimens.[46] In this last study, the most effective second-line strategy was the administration of a bismuth-containing quadruple therapy (either classical or with amoxicillin and levofloxacin); the most effective third-line

strategy was the administration of a not previously used bismuth-containing quadruple therapy; finally, a good alternative as a fourth-line therapy was the administration of rifabutin (PPI, rifabutin, amoxicillin and bismuth).[119]

Is the susceptibility-guided approach cost-effective?

Several studies have evaluated the cost-effectiveness of the susceptibility-guided strategy, generally using decision models. These studies are chronologically reviewed below.

The first cost-effectiveness study was performed by Breuer and Graham in 1999, by using a decision model, and showed that an eradication strategy driven by antimicrobial susceptibility testing would be able to save US $37 per patient treated in a US population.[120] However, it should be noted that, in this study, the empirical group also included the performance of an endoscopy plus biopsy (which may be avoided by the use of non-invasive *H. pylori* diagnostic tests).

In 2003, Romano *et al.* achieved, in a setting of treatment-naïve Italian patients, savings of approximately US $5 per patient in the susceptibility testing group.[66] However, some authors calculated the eradication costs from these data, and pointed out that the mere 5% eradication benefit achieved by an invasive approach may not be justifiable because of the extra cost of US $148/patient for pretreatment susceptibility testing among young dyspeptic patients.[121,122]

In 2013, Cosme *et al.* reported that, in Spain, the culture-based approach was more cost-effective than standard first-line therapy given empirically (€571 *versus* €666 per patient).[77]

In 2007, Furuta *et al.* calculated a similar cost per successful eradication with both strategies in Japan: US $669 per patient for the tailored and US $657 for the standard regimen group.[70]

More recently, in 2018, Liou *et al.* found that, in Taiwan, US $6920 would be required to additionally cure one patient with refractory *H. pylori* infection using the genotypic resistance-guided therapy, compared to empirical therapy, which was obviously not cost-effective.[86]

Also in 2018, Gweon *et al.* showed that the cost of a successful eradication using PCR (US $120) would be similar or superior to the expected cost of a successful eradication with empirical treatment (US $92).[87]

Finally, in 2019, Cho *et al.* reported that, compared with empirical triple therapy, the incremental cost-effectiveness ratios of tailored therapy (using PCR as diagnostic test) were US $3.96 per patient, concluding that, in Korea, tailored eradication may be cost-effective.[93]

In summary, the different studies that have evaluated the cost-effectiveness of the *H. pylori* susceptibility-guided treatment have achieved contradictory results. As *H. pylori* eradication rates depend on several factors (i.e. treatment regimen, compliance, number of prior eradication attempts, among others), the cost-effectiveness of a strategy will also depend on them.[32] In addition, an eradication strategy based on culture consists of several parts, each of which has a precise cost, such as endoscopic procedures and drug regimens.[32] Also, *H. pylori* antibiotic resistance varies among different geographical areas, which may limit the applicability of the results of the cost-effectives analysis to other populations. Furthermore, savings of a strategy are linked with the characteristics of the specific setting; for example, performing pretreatment susceptibility testing in patients with previous, independent indication of upper endoscopy would be obviously more cost-effective.[32] Finally, the cost-effectiveness may vary according to the cost of care in a given country, and therefore the same conclusion may not be applied to other settings.

Conclusion

Resistance of *H. pylori* to antibiotics has reached alarming levels worldwide. Local surveillance networks are required to select appropriate eradication regimens for each region. Tailored treatment of *H. pylori* infection according to systematic antimicrobial susceptibility testing may be useful to limit the emergence of antibiotic resistance worldwide. However, whether patients should systematically undergo an upper endoscopy for bacterial culture (or PCR) before administering *H. pylori* eradication treatment in clinical practice remains a debatable matter. In the present article we have reviewed the advantages and limitations of the susceptibility-guided and the empirical strategies to treat *H. pylori* infection, which are summarized in Table 1.

Table 1. Main advantages and limitations of susceptibility-guided and empirical treatment of *Helicobacter pylori* infection.

Susceptibility-guided treatment	Empirical treatment
Advantages	
Allows performing resistance surveys	"Test-and-treat" strategy for dyspepsia is recommended by all consensus conferences
Provide personalized treatment	Resistance to amoxicillin and tetracycline is extremely rare, so they can be empirically prescribed
Reduce unnecessary antibiotic prescription	No *in vitro* resistance to bismuth has been described, so it can be also empirically prescribed
May limit the emergence of antibiotic resistance worldwide	*In vitro* metronidazole resistance has a limited impact on the efficacy of treatments when sufficiently long treatments and high metronidazole doses are used
Might allow the administration of the standard clarithromycin-based triple therapy to patients with clarithromycin-susceptible strains in areas with high overall clarithromycin resistance	The position in the case of failure is clear: not to re-administer any of the antibiotics against which *H. pylori* has probably become resistant
Molecular tests (PCR) based on a stool sample might enable more convenient methods	Rifabutin and furazolidone are good alternatives for empirical treatment after several eradication failures
It would be recommendable that susceptibility tests are routinely performed in specialized centers, with the aim to evaluate the prevalence of antibiotic resistance in the treatment of naïve patients and the influence of such resistances on the efficacy of treatments	Cumulative *H. pylori* eradication rate with several successive rescue therapies empirically prescribed reaches almost 100%
Limitations	
The moment when it must be performed (before the first treatment or after failure) is controversial	Resistance of *H. pylori* to antibiotics has reached alarming levels worldwide
Implies the performance of endoscopy, which is expensive and uncomfortable	Empirical treatment may increase the emergence of antibiotic resistance worldwide
Low rate of acceptance of endoscopy by patients	In some cases, it will imply prescribing an antibiotic that will lack efficacy
Since the majority of endoscopy findings are normal they do not contribute to management	Increase unnecessary antibiotic prescription
Culture is time consuming	Do not allow performing resistance surveys
Culture is not always available on a routine basis	Do not provide personalized treatment
Culture has low sensitivity (<80%)	May induce transient increase of antibiotic resistance to certain bacteria
Imperfect correlation between susceptibility testing performed by culture and PCR	May induce short-term perturbation of gut microbiota after *H. pylori* eradication
Culture provides useful information only for clarithromycin, metronidazole and quinolones	
Imperfect correlation between *in vitro* and *in vivo* results (mainly for metronidazole)	
Expensive (mainly because of endoscopy)	

PCR, polymerase chain reaction.

It would be recommendable that susceptibility tests (culture or PCR) are routinely performed, even before prescribing first-line treatment, in specialized centers with interest in *H. pylori* management, with the intention to evaluate the prevalence of antibiotic resistance in the treatment of naïve patients and the influence of such resistances on the efficacy of up-to-date first-line eradication treatments. Furthermore, it would also seem recommendable that susceptibility tests are routinely performed in some specialized centers after *H. pylori* eradication failures, to evaluate the development of resistances in this setting and to assess how they may reduce the effectiveness of rescue regimens.

However, the evidence is too limited to support the generalized use of susceptibility-guided therapy for *H. pylori* treatment in routine clinical practice, either as first-line or as rescue treatment. In particular, it seems that despite the use of susceptibility-guided combinations of drugs, rescue treatments are frequently unsuccessful, indicating that other factors different from *in vitro* antibiotic susceptibility influence eradication rates. Practical, economical, and logistical issues should be evaluated and addressed according to the target population and the clinical situation prior to the application of susceptibility-guided *H. pylori* therapy. In the future, stool sample-based molecular approach for detecting *H. pylori* antimicrobial resistance might enable more convenient, less invasive methods that facilitate the applicability of susceptibility-guided treatment.

What is undoubted is that we always must prescribe the most effective first-line *H. pylori* eradication treatments (that is those regimens that have demonstrated to achieve cure rates ⩾90% in our setting) and that the rescue treatment should be carefully chosen depending on which treatment was used initially. The results (*H. pylori* cure rates) of our clinical practice should be continuously audited to confirm that we always maintain a high success rate.

Conflict of interest statement

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