Is Antimicrobial Susceptibility Testing Necessary Before First-line Treatment for *Helicobacter pylori* Infection? —Meta-analysis of Randomized Controlled Trials—

Yuan Wenzhen^{1,2}, Li Yumin³, Guan Quanlin¹, Yang Kehu², Jiang Lei¹,
Wang Donghai⁴ and Yang Lijuan⁵

Abstract

Background With the wide use of antibiotics, antibiotic-resistant *Helicobacter pylori* strains are becoming increasingly prevalent. It has been hypothesized that culture-guided therapy might help to increase treatment success. But the effects and the costs still remain controversial.

Aims To systematically review the efficacy and the cost of culture-guided triple therapy, compared to standard triple regimen for first-line treatment of *Helicobacter pylori* infection.

Methods A search of the Cochrane Library, PubMed, EMBASE, Science Citation Index Expanded and CBM was performed. Randomized controlled trials comparing culture-guided triple therapy to standard triple therapy in the first-line treatment of *Helicobacter pylori* infection were selected for meta-analysis. Relative risk was used as a measure of the effect of two regimens mentioned above with a fixed-effects model using the methods of DerSimonian and Laird.

Results Five randomized controlled trials totaling 701 patients were included. The meta-analysis showed that culture-guided triple therapy was superior referring to a higher eradication rate from intention-to-treat analyses (RR, 0.84; 95% CI, 0.77, 0.90; $p < 0.00001$) and a lower overall cost.

Conclusion Culture-guided triple therapy was more effective than standard triple therapy for first-line treatment of *Helicobacter pylori* infection. Based on the only paper focused on the overall cost, the culture-guided triple therapy was also more cost saving. Antimicrobial susceptibility testing is necessary before first-line treatment for *Helicobacter pylori* infection.

Key words: *Helicobacter pylori*, first-line treatment, culture-guided triple therapy, standard triple therapy, overall cost, Meta-Analysis

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Introduction

Helicobacter pylori (*H. pylori*) is a highly prevalent chronic infection with a worldwide prevalence of nearly 50%, U.S. prevalence of 30-40% (1, 2), and Chinese prevalence of 45% (3). *H. pylori* is known to play a major contributory role in the pathogenesis of chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue (MALT)

lymphoma and distal gastric cancer (4-6).

Although various antimicrobial regimens have been proposed and tested, the regimen combining a proton pump inhibitor or ranitidine bismuth citrate with two antibiotics for 7 to 14 days triple therapies is the recommended first-line treatment for *H. pylori* infection (7-9). This standard therapy presents eradication rates of *H. pylori* from 60% up to 90% (10-13), and the major obstacle to 100% effective therapy being represented by antimicrobial-resistant *H. pylori*

¹The first hospital of Lanzhou University, Lanzhou, China, ²The Evidence-Based Medicine Center of Lanzhou University, Lanzhou, China, ³The second hospital of Lanzhou University, Key laboratory of digestive system tumors, Gansu province, Lanzhou, China, ⁴Montefiore Medical Center, Albert Einstein College of Medicine, New York, U.S.A. and ⁵The school of Economics of Lanzhou University, Lanzhou, China

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Correspondence to Dr. Li Yumin, liyumin168@yahoo.com.cn

strains (12, 14). Metronidazole resistance was the first to be described (15, 16) and clarithromycin resistance was another key factor (17). In recent reports, resistance ranged from 10% to 50% for metronidazole and 0% to 15% for clarithromycin in Europe (18, 19), whereas, in the USA, 37% for metronidazole and 10% for clarithromycin (20), and it varies widely amongst different ethnic groups (20, 21).

However, with the wide use of such antibiotics, antibiotic-resistant *H. pylori* strains are becoming increasingly prevalent (14). Several studies have evaluated the relationship between pre-treatment antibiotic resistance and eradication rate using different standard treatments and performing a susceptibility test before the initiation of the therapeutic regimen (22-25). Accumulating evidences [included randomized controlled trials (RCTs)] suggest antibiotic sensitivity testing results in improving eradication rate (26-31). Nevertheless, the effects still remain controversial (32-34). Furthermore, whether or not culture-guided therapy is cost saving is another bone of contention, compared to standard treatment (30, 31, 35, 36).

We systematically reviewed all RCTs and carried out a meta-analysis to assess whether a culture-guided triple therapy (chosen based on a preliminary *in vitro* susceptibility test), and a standard triple therapy could improve the eradication rate in patients affected by *H. pylori* infection and to assess which regimen is cost saving.

Patients and Methods

Study selection criteria

The titles and abstracts of all citations identified by the literature search were reviewed. Selection criteria were then applied to all potentially relevant studies. The selection criteria for inclusion in the meta-analysis were: (i) RCTs (included quasi-randomized controlled trials) comparing two first-line therapies; (ii) They had to include at least two branches of treatment consisting of (a) standard triple therapy that included a proton pump inhibitor or a ranitidine bismuth citrate with two antibiotics for 7 to 14 days, and (b) culture-guided triple therapy that included a proton pump inhibitor or a ranitidine bismuth citrate with two antibiotics chosen based on susceptibility testing for 7 to 14 days; (iii) Confirmation of *H. pylori* eradication at least 4 weeks after completion of treatment; (iv) The confirmation of infection based on urea breath testing.

Search strategy for identification of studies

Trials were identified by searching the Cochrane Library (Issue 4 2008), PubMed (December 2008), EMBASE (December 2008), Science Citation Index Expanded (December 2008), and CBM (Chinese Biomedical Literature Database) (December 2008). A search strategy was constructed by using a combination of the following words: (*Helicobacter pylori* OR *H. pylori*) AND (culture OR susceptibility OR antimicrobial sensitivity OR *in vitro* susceptibility testing OR an-

tibiotic). Articles published in any language were included. Reference lists from the trials selected by electronic searching were hand searched to identify further relevant trials. Abstracts of the articles selected in each of these multiple searches were reviewed and those meeting the inclusion criteria were recorded. In the case of duplicate reports, or studies obviously reporting results from the same study population, only the latest published results were used.

Assessment of study quality

Two investigators (Yuan Wenzhen and Li Yumin) conducted the search independently and they also evaluated study quality using the simple method that is recommended by the Cochrane Handbook (37). Quality assessment of studies was performed independently by two reviewers (Yuan Wenzhen and Li Yumin). Discrepancies in the interpretation were resolved by consensus.

Data extraction

Two investigators (Yuan Wenzhen and Li Yumin) extracted the data from the studies meeting the selection criteria. Data were extracted concerning (a) study design; (b) age and gender of patients enrolled in the study; (c) number of patients enrolled in the study; (d) testing used to confirm persistent infection prior to study enrollment and the eradication after treatment; (e) drug regimen, including specific doses and treatment duration; (f) number of patients in which *H. pylori* infection was successfully eradicated (either directly provided or calculated given the intention-to-treat and per-protocol analyses); and (g) the overall cost of each regime (including the cost of office visits, endoscopy plus biopsy, rapid urease test, histology, culture and antimicrobial susceptibility testing, ¹³C-urea breath test, and cost of drugs). The following variables were also extracted: year of publication, format (abstract or journal article).

Statistical analysis

The primary study outcome for the meta-analysis was the eradication rate of standard triple therapy compared to culture-guided triple therapy, and the overall cost of each regime was the second outcome. Following data extraction, eradication rates from intention-to-treat (ITT) analyses and per-protocol (PP) analyses were entered into Review Manager 5.0 software programs (Cochrane Collaboration) for the performance of meta-analysis. In summarizing the data from these comparative trials, risk ratio (RR) was used as the measure of association, and summary relative RRs along with its 95% confidence interval (CI) were calculated based on a fixed-effects model using the methods of DerSimonian and Laird (38). A test of heterogeneity was also performed using the I^2 statistic to establish if any clinical, methodological, or statistical variability existed among the studies used in meta-analysis. Statistical significance for the test of heterogeneity was set at 0.10. The same method of meta-analysis was applied to the overall cost of each regime.

Figure 1. The flowchart of study selection.

Table 1. Quality Assessment of Included Studies (28-32)

Study (Country)	Randomization	Allocated Concealment	Blinding	Withdrawal/lost to follow-up	Follow-up Time (w)	Dropout (n)
Wang 2008 China	Quasi-Random	Unclear	Not described	Described	4 w	9
Neri 2003 Italy Ramano	Unclear	Unclear	Not described	Described	8 w	10
2003 Italy Tarocchio	Adequate	Unclear	Not described	Described	12 w	4
2000 Italy Ramano	Quasi-Random	Unclear	Not described	Described	4 w	8
2000 Italy	Unclear	Unclear	Not described	Described	12 w	2

w, Week; n, number

Results

The flowchart of reviews showed the detailed process of selection (Fig. 1). Of the six potential eligible articles, we excluded another one which focused on second-line treatment for *H. pylori* infection (39). Five RCTs (n=701 patients) were included at last (28-32). The quality of the included studies is shown in Table 1. The included patients did not differ in baseline characteristics (see Table 2).

The results of the five studies are summarized in Table 3. A meta-analysis of the eradication rates with ITT and PP analyses demonstrated superiority of the culture-guided triple therapy to standard triple therapy (RR, 0.84; 95% CI, 0.77, 0.90; $p < 0.00001$ and RR, 0.83; 95% CI, 0.78, 0.89; $p < 0.00001$, respectively) (see Figs. 2, 3).

Only one article focused on the overall cost of culture-guided triple therapy and standard triple therapy (31). The result was approximately \$5 U. S. saving per patient compared with standard triple therapy, even with the supplementary cost of culture and testing.

Discussion

Antimicrobial drug resistance can be either primary (i.e., existing before therapy) or secondary (i.e., developing as the result of failed therapy). Secondary resistance is largely responsible for the decline in eradication rates, and yet the results of comparative studies of different therapies for *H. pylori* infection that have produced very low cure rates continue to be described as equivalent to one another and as acceptable therapy (40-42). Therefore therapies for *H. pylori* infection were largely derived by using a 'hit or miss' process (43). Recently, Pilotto et al warned that the incidence of secondary *H. pylori* resistance to metronidazole and/or clarithromycin in treatment failures after 1-week proton pump inhibitor-based triple therapies was approximately 70% (44). Obviously, one of the main goals today in *H. pylori* therapy is to decrease the number of eradication failures as best as possible (45).

To solve this problem, pretherapy antibiotic sensitivity testing is one of the most promising ways, which has been suggested in high antibiotic resistance regions (23, 46), in

Table 2. Characteristics of Included Studies (28-32)

Study	Study Design	Test Confirming Infection	Test Confirming Eradication	Male/female(n)		Age (mean±SD)		SUSC		SG		SUSC		Treatment Regimen doses /Duration		Duration assed the eradication	
				SG	SUSC	SG	SUSC	SG	SUSC	SG	SUSC	SG	SUSC				
Wang 2008 China	RCT	both histology and RUT positive	histology and RUT or 14C-UBT	39/41	21/19	Mean±SD 41.6±8.8	Mean±SD 40.1±10.4	OAC 1/w or OAM* 1/w	OAC 1/w or OAM* 1/w	OAC 1/w or OAM* 1/w	OAC 1/w or OAM* 1/w	OAC 1/w or OAM* 1/w	OAC 1/w or OAM* 1/w	O 20 mg bid and two sensitive antibiotics (AM* or AF or AL or FC or LC) 1/w		4w	
Neri 2003 Italy	RCT	RUT, histology and culture.	13C-U BT	54/68	58/62	Mean 48	Mean 54	OAC 1/w or BCT 1/w	OAC 1/w or BCT 1/w	OAC 1/w or BCT 1/w	OAC 1/w or BCT 1/w	OAC 1/w or BCT 1/w	OAC 1/w or BCT 1/w	Without resistance or resistance to TIOAC 1/w Resistance to COAT 1/w or Without resistance PCT Resistance to CBAT 1/w or resistance to TBCA 1/w		8w	
Ramano 2003 Italy	RCT	Both histology and RUT positive	13C-U BT	52/23	49/26	Range 21-26, Mean 32	Range 22-60, Mean 34	OMC 1/w	OMC 1/w	OMC 1/w	OMC 1/w	OMC 1/w	OMC 1/w	Without resistance OMC 1/w Resistance to COAM 1/w Resistance to MOAC 1/w Resistance to C and MBAT 2w		12 w	
Tanocchio 2000 Italy	RCT	RUT, histology and culture.	13C-U BT	22/34	29/24	Range 42-74, Mean 58	Range 19-81, Mean 50	OTC 1/10d	OTC 1/10d	OTC 1/10d	OTC 1/10d	OTC 1/10d	OTC 1/10d	Without resistance OTC 1/10d Resistance to COTIA 1/10d Resistance to TIOAC 1/10d Resistance to both C and TIOA 1/10d		4w	
Ramano 2000 Italy	RCT	Both histology and RUT positive	13C-U BT	25/15	27/13	Range 24-60, Mean 35	Range 22-59, Mean 34	OMC 1/w	OMC 1/w	OMC 1/w	OMC 1/w	OMC 1/w	OMC 1/w	Without resistance OMC 1/w Resistance to COAM 1/w Resistance to MOAC 1/w Resistance to C and MOBAT 2w		12 w	

A, amoxicillin 1 g bid; B, bismuth citrate 125 mg qid; C, Clarithromycin 500mg bid; d, day; F, Furazolidone 100mg bid; L, levofloxacin 200mg bid; M, metronidazole 500mg bid; O, omeprazole 20mg bid; SG, Standard group; SUSC, susceptibility test group; T, tetracycline 500mg qid; Ti, tinidazole 500mg bid; UBT, urea breath test; w, week

younger patients who are more likely to have been exposed to those drugs and more likely to experience treatment failure, (47, 48) and in children with recurrent abdominal pain or other symptoms compatible with *H. pylori* infection (49-51).

Neri et al questioned the importance of bacterial resistance to antibiotics in determining the reduction in *H. pylori* eradication efficacy (32). They stressed that many other factors influence the eradication rates of anti-*H. pylori* treatments, such as alcohol consumption, gender, smoking status, age, type and severity of gastritis (52), lack of gastric drug-induced alkalization (53), bacterial load (54) and the persistence of the bacterium in inaccessible sanctuaries (55). Faber et al questioned the cost-effectiveness of sensitivity-based treatment after constructing a hypothetical arithmetical model and the result was that only 5% of the patients are expected to benefit from culture-guided therapy (33). Qasim et al calculated the eradication costs from data provided by Romano et al, and pointed out that the mere 5% eradication benefit achieved by an invasive approach may not be justifiable for the extra cost of \$148/patient for pretreatment susceptibility testing among young dyspeptic patients (36).

Our study shows that, standard triple therapy eradicated *H. pylori* infection in 75% of patients, and personalized therapy in patients affected by *H. pylori* infection significantly enhanced the eradication rate to values that were close to 90%. Ideally, the regimen should be based on pretreatment drug susceptibility testing, just as in other bacterial infectious diseases (43). Only by this way clinicians can predict treatment success and the development of resistance to therapy in the community is quickly recognized, which results in rapid changes in practice to maintain excellent results.

In spite of this, the routine use of endoscopy is not feasible since it is expensive and not well-tolerated by all patients. Other less invasive and less expensive methods need to be designed for collecting specimens of *H. pylori* and for culturing it (56).

This is the first meta-analysis comparing culture-guided triple therapy versus standard triple therapy for the treatment of *H. pylori* infection. Several methodological weaknesses may limit the validity and generalizability of this meta-analysis. Initially, of the six included studies, two of them are Quasi-RCTs, none of them mentioned double blind, without which it is possible to produce high performance bias and measuring bias; none of them mentioned allocation concealment, without which might bring selective bias in these trials, because it was possible for those responsible for recruiting the participants to alter their assignment if allocation was concealed. There is also the theoretical concern for publication bias in favor of new therapy. Lastly, there are no studies involving patients from America, Africa or Japan. The studies included were conducted in Italy and China. It is well established that antibiotic resistance profiles of *H. pylori* vary among different geographical regions as pharmacogenomic difference could exist (15), which may limit the

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