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Management of Helicobacter pylori *in duodenal ulcer: a cost-effectiveness analysis*

A. GARCÍA-ALTÉS*, A. J. JOVELL*†, M. SERRA-PRAT* & M. AYMERICH*
**Catalan Agency for Health Technology Assessment and Research; and †Fundació Biblioteca Josep Laporte, University Autonoma of Barcelona, Barcelona, Spain*

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SUMMARY

Background: Empirical eradication therapy of *H. pylori* has been proposed as a therapeutic alternative for duodenal ulcer.
Aim: To identify the cost-effectiveness of empirical eradication therapy vs. test-and-treatment for the management of patients already diagnosed with a duodenal ulcer.
Methods: A decision analysis was performed to compare the cost-effectiveness of empirical eradication therapy of *H. pylori* diagnosed duodenal ulcer vs. eradication therapy after confirmatory diagnosis of *Helicobacter pylori* infection by means of several diagnostic tests.
Results: The empirical eradication therapy of duodenal ulcer was found to be the most effective and cost-effective strategy of all the alternatives. Amongst the alternatives, which included the previous performance of confirmatory diagnostic tests, the best cost-effectiveness ratio used a serology test. The model was robust in the face of changes in the values of therapeutic effectiveness, sensitivity and specificity of the diagnostic tests, prevalence of *H. pylori* infection in duodenal ulcer, duration of the antisecretory therapy, and number of medical visits.
Conclusions: Based on our cost-effectiveness analysis, a treat approach is more effective and cost-effective than a test-and-treat approach in the clinical management of already diagnosed duodenal ulcer.

INTRODUCTION

Peptic ulcer is a very common disease, with an annual incidence of between one and three per 1000 inhabitants in developed countries, and which affects between 5% and 10% of the population at some time in their lives.[1–3]

The association of peptic ulcer with the bacterium *Helicobacter pylori* was first documented in 1983.[4] Currently, there is good quality evidence to assert that infection by *H. pylori* is an important cofactor in the pathogenesis of most duodenal ulcers, and that its eradication is associated with a decrease in the number of both ulcer relapses and bleeding events.[5–7]

The multiple therapeutic approaches for duodenal ulcer include several drugs, such as antisecretives, H_2-receptor antagonists, antacids, and antibiotics, which may be given alone or in combination up to a quadruple schedule, in different dosages, and for different time periods. All these factors are sources of great variability in primary care practise in the treatment of duodenal ulcers, which might lead to differences in therapeutic effectiveness, accessibility to diagnostic tests, equity of care, and use of resources associated with the management of this clinical condition. Anti-ulcer drugs ranked in Spain amongst the 10 highest selling drugs.[8]

The high prevalence of duodenal ulcer, the number of primary care visits associated with this condition, and drug-related expenses, have increasingly raised

Correspondence to: Dr A. García-Altés, Catalan Agency for Health Technology Assessment and Research, Travessera de les Corts, 131–159, Pavelló Ave Maria, 08028 Barcelona, Spain.
E-mail: annaga@olimpia.scs.es

concerns about the effectiveness and efficiency of the different strategies for the clinical management of duodenal ulcers. The empirical eradication therapy has been proposed as the therapeutic alternative for duodenal ulcer.

The objective of this study is to identify whether treatment without testing, or testing-and-treatment is the most cost-effective option for the clinical management of recurrent duodenal ulcer.

MATERIALS AND METHODS

A decision analysis was performed to compare the cost-effectiveness of empirical eradication therapy of diagnosed duodenal ulcer, and the eradication therapy selected after confirmatory diagnosis of *H. pylori* infection by means of several diagnostic tests. Empirical eradication therapy consisted of treating a patient with a previous background of non-complicated duodenal ulcer, without doing a test for *H. pylori* infection. The eradication therapy considered was triple therapy with clarithromycin plus amoxicillin or an imidazole administered for 1 week, and omeprazole for 2 weeks. This therapy was chosen because there is scientific evidence of its higher effectiveness compared with other eradication therapies.[9–11]

Figure 1 describes the decision tree used to perform the cost-effectiveness analysis. The decision model considers patients with endoscopically proven, uncomplicated active duodenal ulcer disease, who are not currently taken antisecretory medication and have not previously received *H. pylori* eradication therapy. At the first decision node, the physician should decide between an empirical eradication therapy or a diagnostic test aimed at confirming the suspicion of *H. pylori* infection, and thus, be able to start a specific therapy. In case of selecting the empirical eradication therapy, the physician would prescribe eradication therapy ignoring the patient's *H. pylori* infection status.

The second alternative was the performance of a diagnostic test, such as a urea breath test, serology test, urease test, culture or histology. The results of the tests depended on the existence of infection, and on their sensitivity and specificity values. In case of a positive result (either true-positive or false-positive),

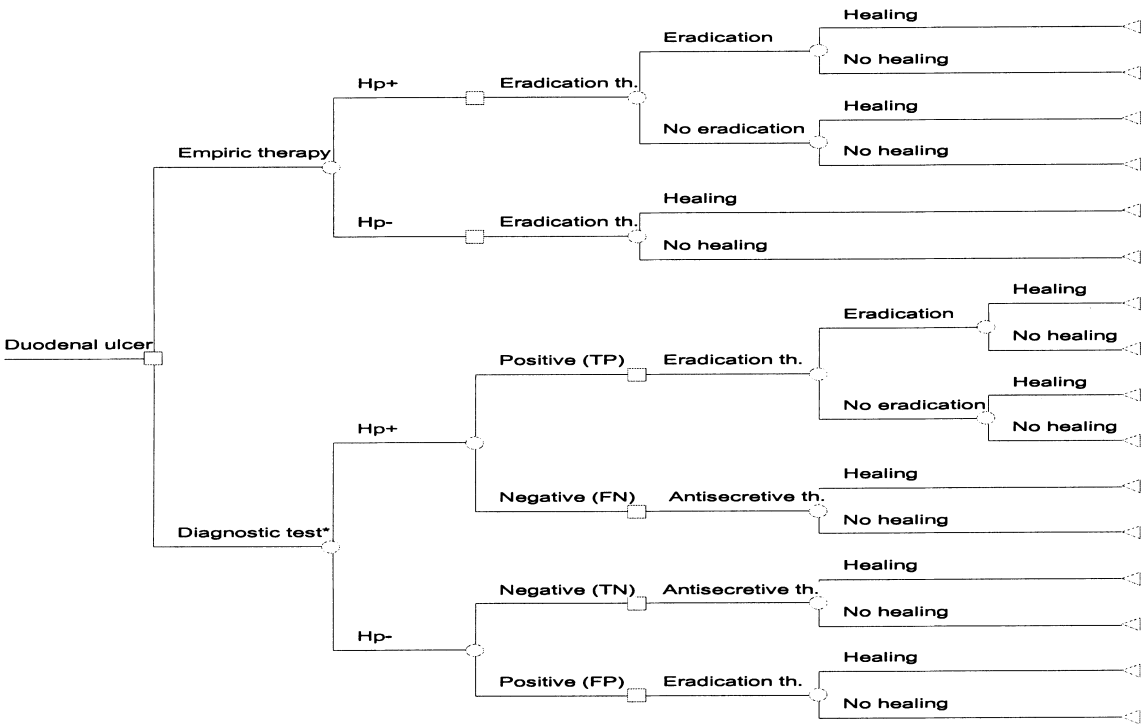

Figure 1. Decision tree model. Hp +, *H. pylori*-positive; Hp –, *H. pylori*-negative' Eradication th, Eradication therapy; Antisecretive th, Antisecretive therapy; TP, True positive; FP, False positive; TN, True negative; FN, False negative. Diagnostic test included either urea breath test, serology test, urease test, culture or histology.

the patient received an eradication therapy, and in case of negative result (either true-negative or false-negative), the patient received antisecretive therapy. In order to build up the decision analysis model, the information listed in Table 2 was included in the model.

Effectiveness of the therapies

Therapeutic effectiveness has been measured as the rate of healed duodenal ulcers and eradicated infections 1 month after the end of the treatment. The studies considered to produce the best quality data were those randomized controlled trials including clarithromycin, amoxicillin or an imidazole, and omeprazole as experimental therapy.[12–16] The effectiveness values of the antisecretive treatment were also obtained from randomized controlled trials, including omeprazole as a control treatment.[13, 17, 18]

Sensitivity and specificity values of the diagnostic tests of H. pylori *infection*

The diagnostic accuracy values of the diagnostic tests considered in this study and their corresponding data sources are listed in Table 1.

Prevalence of H. pylori *in duodenal ulcer*

The adopted baseline reference value was a 95% prevalence of *H. pylori* in duodenal ulcer.[19] However, a value of 85.9% obtained in the literature from Spain, and a minimum prevalence of 60% have also been considered in the sensitivity analysis.[20, 21]

Table 1. Baseline reference values

Variable	Reference value	Range	Source of evidence (Reference number)
Eradication with eradication therapy	87.2%	(84.5–89.8)	12, 14–16
Healing with eradication therapy	92.6%	(89.1–96.1)	12–16
Healing with antisecretive therapy	88.9%	(82.7–95.1)	13, 17, 18
Sensitivity urea breath test	95%	90–100	33, 35, 1034
Specificity urea breath test	90%	85–100	10, 30, 37, 3136
Sensitivity serology test	85%	70–96	10, 38
Specificity serology test	79%	70–96	10, 35
Sensitivity urease test	85%	80–95	10, 30
Specificity urease test	90%	85–100	10, 30
Sensitivity culture	90%	75–95	10
Specificity culture	99%	98–100	30, 31, 40–42, 1039
Sensitivity histology	95%	85–98	10, 30
Specificity histology	95%	90–100	43
Prevalence of *H. pylori*	95%	60–95	19–21
Cost of eradication therapy	157.98	—	24
Cost of antisecretive therapy	112.39	—	24
Cost of digestive endoscopy and biopsy	23.42	—	22, 23
Cost of urea breath test	24.98	—	Pers. comm.
Cost of serology test	9.37	—	Pers. comm.
Cost of urease test	3.12	—	22, 23
Cost of culture	12.49	—	22, 23
Cost of histology	19.98	—	22, 23
Cost of visit to general practitioner	19.70	—	22, 23
Cost of visit to specialist	34.34	—	22, 23

Data in parentheses indicate 95% confidence interval.
Data without parentheses indicate maximum and minimum reference values obtained in the literature.
Costs in 2000 US$.

Cost of the clinical management strategies

Since the perspective of analysis used was that of the public health care payer, only direct costs were included in the analysis. These corresponded to: the cost of the diagnostic tests; the cost of the visits to a primary care practitioner and to a gastroenterologist; and the cost of drugs. In the empirical eradication therapy alternative, one visit to the primary care practitioner was included. In the test-and-treat alternative, one visit to the primary care practitioner, one visit to the specialist who would check the tests results, and a second visit to the primary care practitioner who would prescribe a specific treatment were included. The cost of both diagnostic tests and medical visits was estimated from 1997 administrative data from the Catalan Health Service—the public financing system.[22, 23] For the estimation of the cost of drug therapies, an eradication therapy comprising clarithromycin (500 mg every 12 h for 1 week), amoxicillin (1000 mg every 12 h for 1 week), and omeprazole (20 mg every 12 h, for 2 weeks) was considered. Also considered was an antisecretive therapy of omeprazole (20 mg every 12 h for 2 weeks). Reference list prices of these drugs were used as a measure of the cost of the different therapies.[24] As all costs were in 1997 Spanish pesetas, costs were actualized and converted to 2000 US$.

The measures of the economic analysis were cost per healed duodenal ulcer and cost per eradicated infection, valued in 2000 US$. The time horizon established was 1 month post-therapy, and no discount rate was used since costs and benefits occurred in a period shorter than 1 year. Different sensitivity analyses were performed to test for the robustness of both the model, and the results obtained against variations in the baseline analysis assumptions. Data were modified in the following variables, for the sensitivity analysis: therapeutic effectiveness; sensitivity and specificity values of the diagnostic tests; prevalence of *H. pylori* in duodenal ulcer; duration of the administration of antisecretive therapy; and number of medical visits. Data analysis was performed with Data 3.0 for Windows software package.

RESULTS

The empirical eradication therapy of patients already diagnosed with an uncomplicated active duodenal ulcer was found to be the most cost-effective strategy of all the studied alternatives. Amongst the alternatives, which included the previous performance of a confirmatory diagnostic test, the best cost-effectiveness ratio, measured as the smallest cost per healed duodenal ulcer, used a serology test, the next most cost-effective being those including a urease test, and urea breath test. The strategies with the worst cost-effectiveness ratio were those requiring the performance of culture and histology tests (Table 2). It should be noted that the strategy of empirical eradication therapy was also the most effective.

Table 2. Results of the baseline analysis

Alternative	Cost/HDU	%HDU	Cost/EI	%EI
Empirical therapy	192.20	92.4%	203.56	82.8%
Serology test	253.28	91.9%	265.96	78.7%
Urease test	271.64	91.9%	285.33	70.4%
Urea breath test	273.64	92.2%	288.99	70.4%
Culture	283.46	92.0%	298.51	74.5%
Histology	293.48	92.2%	309.95	78.7%

HDU: Healed duodenal ulcer.
EI: Eradicated infection.
%HDU: Percentage of healed duodenal ulcers in each alternative.
%EI: Percentage of eradicated infections in each alternative.
Costs in 2000 US$.

In terms of cost per eradicated infection, the empirical eradication therapy was the most cost-effective, compared to clinical management strategies involving previous confirmatory diagnostic tests. The relative rank of alternatives, including previous confirmatory tests, was identical to the above-mentioned analysis. Additionally, in this case, the alternative of empirical eradication therapy was the most effective.

The one-way sensitivity analyses performed, modifying the therapeutic effectiveness, diagnostic accuracy of tests, and prevalence of *H. pylori* infection in duodenal ulcer, showed the robustness of the results to changes in the selected values. Empirical eradication therapy was still the most effective alternative, and the relative rank of the cost-effectiveness ratios of the alternatives, involving diagnostic confirmatory tests, was maintained (Table 3). A threshold analysis was performed in order to estimate the minimum prevalence of *H. pylori* infection in duodenal ulcer for empirical treatment to be cost-effective. With 0% prevalence of *H. pylori* infection in duodenal ulcer, the empirical eradication therapy was still the most cost-effective alternative (Table 3).

Table 3. Results* of the sensitivity analysis

Clinical scenario	Empirical eradication	Serology	Urease test	Urea breath test	Culture	Histology
1	192.20	253.28	271.64	273.64	283.46	293.48
2(a)	185.56	245.76	263.56	264.63	274.59	283.82
2(b)	199.33	261.26	280.24	283.28	292.93	303.83
3	198.75	257.93	274.92	281.52	290.14	301.93
4(a)	192.20	257.59	275.40	275.55	285.29	294.67
4(b)	192.20	247.22	269.55	271.57	277.99	289.78
5(a)	192.91	251.18	269.02	270.77	280.38	290.45
5(b)	194.95	245.13	261.59	262.47	271.51	281.71
5(c)	199.86	230.68	244.36	242.60	250.28	260.76
6	131.41	192.13	210.50	212.74	222.44	232.58
7	192.20	194.47	234.66	215.07	246.17	256.26
8	135.89	135.78	176.48	158.60	189.50	200.98

*Values in $ per healed duodenal ulcer.
Setting 1: Results of the base case.
Setting 2: Results of the sensitivity analysis using the (a) maximum and (b) minimum effectiveness values for all therapies.
Setting 3: Results of the sensitivity analysis using the maximum effectiveness value of the antisecretive therapy and the minimum effectiveness value of the eradication therapy.
Setting 4: Results of the sensitivity analysis using the (a) maximum and (b) minimum diagnostic accuracy data of diagnostic tests.
Setting 5: Results of the sensitivity analysis using (a) the prevalence value referred in Spain of *H. pylori* in duodenal ulcer of 85.9% (b) a prevalence of 60%, and (c) a minimum prevalence of 0%.
Setting 6: Results of the sensitivity analysis considering duration of the antisecretive therapy of 1 week.
Setting 7: Results of the sensitivity analysis considering the inclusion of a single visit to the primary care practitioner.
Setting 8: Results of the sensitivity analysis using the maximum effectiveness of the antisecretive therapy and the minimum effectiveness of eradication therapy, duration of antisecretive therapy of 1 week and inclusion of a single visit to the primary care practitioner.

The duration of the antisecretive therapy has also been changed, for example the administration of omeprazole for 1 week both in triple therapy and in antisecretive therapy, since there was evidence of a similar effectiveness compared with 2-week therapy.[25] Again, the results obtained were robust, although the cost per healed duodenal ulcer decreased by 20–30% (Table 3).

Another sensitivity analysis included the cost of one single general practitioner visit for those alternatives, including the previous performance of confirmatory diagnostic tests. Results remained stable, although the cost-effectiveness values were more similar to those obtained using the empirical eradication therapy (Table 3).

In order to assume the most unfavourable clinical scenario for empirical eradication therapy, a multiple-way sensitivity analysis has been performed. This considers: the best effectiveness value for antisecretive therapy; the worst effectiveness value for eradication therapy; administration of omeprazole for 1 week in both antisecretive and eradication therapies; and a single visit to the primary care practitioner for all alternatives. In this case, the rank of alternatives changed: serology test and guided treatment was the most efficient alternative, followed by empirical therapy and urea breath test. Here, the least efficient alternatives were those including endoscopy (Table 3).

DISCUSSION

The results of the analyses performed showed that an empirical eradication therapy of diagnosed duodenal ulcer was more cost-effective, compared with alternatives involving a confirmatory diagnostic test before the start of the therapy. These results agreed with those obtained by Imperiale *et al.* in an economic analysis performed in a health care context which was quite different from the public financing system of Spain.[26]

The lowest effectiveness of the alternatives performing confirmatory diagnostic tests was due to the lack of a

100% diagnostic accuracy of the tests which yielded false results. Additionally, the high cost of these alternatives was due, aside from the cost of the test itself, to the cost of a visit to a specialist and of a further visit to the primary care practitioner. These costs exceed that of eradication therapy compared to antisecretive therapy in *H. pylori*-positive patients. The greater effectiveness and lower cost associated with the empirical eradication therapy strategy make it pointless to perform an incremental analysis regarding this alternative.

The decision analysis model was robust in the face of changes in therapeutic effectiveness, in the sensitivity and specificity of the diagnostic tests, in the prevalence of *H. pylori* infection in duodenal ulcer, in the duration of the antisecretive therapy, and in the number of medical visits. It can be concluded from the sensitivity analyses performed, that the relative rank of the alternatives did not depend on the prevalence of the infection, nor on the sensitivity and specificity values of the diagnostic tests. This is because the cost of diagnostic tests for all of the population with duodenal ulcer was by far higher than the savings that may be made by screening the population with duodenal ulcer, and treating them depending on test results.

The duration of the antisecretive therapy, however, is an important parameter in interpreting the scope of the results. The administration of omeprazole for only 1 week in lieu of 2 weeks, both in antisecretive therapy and in the cases of triple therapy combinations, reduced the cost per healed duodenal ulcer by between 20% and 30%.

The sensitivity analysis performed which considered only one visit to the general practitioner should also be discussed separately. In this case, the cost-effectiveness ratio of all the alternatives involving diagnostic tests was lower. This assumption, whilst absurd in those cases involving endoscopy, made sense when assessing the usefulness of non-invasive tests that can be performed quickly in primary care, such as the urea breath test. Although the empirical eradication therapy was still the most efficient alternative in the management of a duodenal ulcer, these kind of tests may only be efficient in high-risk patients.[27]

In only one of the analysed cases, an alternative involving a confirmatory diagnostic test was more efficient than the empirical eradication therapy. This involved the results of a serology test in the clinical scenario, with the highest effectiveness of the antisecretive therapy, the lowest effectiveness of eradication therapy, 1 week treatment with omeprazole, and a single visit to the general practitioner. However, this is a very unlikely scenario, since the results of this diagnostic test are rarely obtained at the first visit.

Economic analyses in general—this one being no exception—present different limitations associated with the baseline assumptions used in decision models, and in defining the baseline clinical–economic settings of care. First, the analysis starting point was the presence of an endoscopically proven uncomplicated active duodenal ulcer. Dyspepsia has not been used as a starting point (as it has been in other studies). This is due to the unspecific definition of this clinical condition or symptom, to the lack of scientific evidence on the efficacy of eradication therapy in this condition, and to the problem of bacterial resistance implied by the indiscriminate adoption of antibiotic therapies.[7, 28–32] Gastric ulcers have been excluded, since diagnosis should include endoscopy and biopsy to rule out gastric cancer, and these tests allow physicians to check for *H. pylori* infection status.

Second, the decision analysis designed had explicitly adopted percentages of compliance with the therapies, and diagnostic test uptakes of 100%. Although it actually may not be the case, one of the possible advantages of triple therapy is that it might favour therapeutic compliance since duration of the treatment is only 1 week. The risks associated with the performance of any of the specific diagnostic tests were not considered in the analysis, neither were the adverse effects of antibiotics or endoscopy taken into consideration. In this sense, the inclusion of patients' preferences regarding the different diagnostic tests may be an interesting research area, using the most recently published scientific evidence and applying cost-utility analysis.

Third, since the analysis was carried out from the perspective of the payer of the public health care financing system, the costs used were public tariffs which may not reflect the true cost of the alternatives, but could actually reflect the amount the payer was willing to pay for their performance. This analysis could also be performed from a less conservative perspective, using the payment standards of other health care systems, or the prices used by private third payers. In particular, with the latter, the results would favour, even more highly, the alternative of empirical therapy, since the prices fixed by

private institutions for the payment of diagnostic tests were much higher than public tariffs. However, accounting cost databases reflecting the real cost of the resources used, and the consequences of the interventions analysed, would make it possible to increase the validity, reliability, reproducibility, comparability, credibility and transparency of cost-effectiveness analyses.

Additionally, since the perspective of analysis used was that of the public health care payer, instead of the societal perspective, no indirect costs (or named productivity losses) were included in the model. It is likely that productivity losses would have been greater with the test-and-treat option than with the empirical treatment option, since it includes more physician visits, further supporting the empirical treatment approach.

Fourth, the outcome measure used and the available scientific evidence led to use a time horizon of 1 month post-therapy in the analysis. This fact is relevant since, on the one hand, it implies the inclusion of alternative or complementary therapies in case the first therapy fails. On the other hand, it means not considering relapses or worsening of *H. pylori* infection, and/or resistances to the antibiotics used. In case of scientific evidence on these variables, a longer time horizon should be used in order to include all negative consequences of the therapy.

In the future, specific studies which take into account the limitations found in this study should be designed, regarding both the quality of scientific evidence on effectiveness data, and the validity of the assumptions of the baseline analysis and the measured costs. The proposed model should be validated in primary care, to see whether it really reflects valid and reliable standards of care, and whether the initial assumptions of the model were confirmed.

As long as this analysis reflected the conditions of standard care clinical practise in Spain, and the cost patterns by which services were purchased, the results of this analysis allows us to recommend the adoption of empirical eradication therapy administered for 1 week as a first therapeutic option in the clinical management of an endoscopically proven uncomplicated active duodenal ulcer. Therefore, based on our cost-effectiveness analysis, a treat approach was more effective and cost-effective than a test-and-treat approach in the clinical management of already diagnosed duodenal ulcer.

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