Economic evaluation of test-and-treat and empirical treatment strategies in the eradication of Helicobacter pylori infection: A Markov model in an Iranian adult population

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Received: 18 April 2015 Accepted: 15 September 2015 Published: 14 February 2016

Abstract
Background: Helicobacter pylori may cause many gastrointestinal problems in developing countries such as Iran. We aimed to analyze the cost-effectiveness and cost-utility of the test-and-treat and empirical treatment strategies in managing Helicobacter pylori infection.

Methods: This was a Markov based economic evaluation. Effectiveness was defined as the symptoms free numbers and QALYs in 100,000 hypothetical adults. The sensitivity analysis was based on Monte Carlo approach.

Results: In the test-and-treat strategy, if the serology is the first diagnostic test vs. histology, the cost per symptoms free number would be 291,736.1 Rials while the cost per QALYs would be 339,226.1 Rials. The cost per symptoms free number and cost per QALYs when the 13 C-UBT was used as the first diagnostic test vs. serology was 1,283,200 and 1,492,103 Rials, respectively. In the empirical strategy, if histology is used as the first diagnostic test vs. 13 CUBT, the cost per symptoms free numbers and cost per QALYs would be 793,234 and 955,698 Rials, respectively. If serology were used as the first diagnostic test vs. histology, the cost per symptoms free and QALYs would be 793,234 and 368,941 Rials, respectively.

Conclusion: There was no significant and considerable dominancy between the alternatives and the diagnostic tests.

Keywords: Cost-Effectiveness Analysis, Cost-Utility Analysis, Gastric Acid Anti-Secretory Treatment, Helicobacter Pylori Infection.

Cite this article as: Mazdaki A, Ghiasvand H, Sarabi Asiabar A, Naghdi S, Aryankhesal A. Economic evaluation of test-and-treat and empirical treatment strategies in the eradication of Helicobacter pylori infection; A Markov model in an Iranian adult population. Med J Islam Repub Iran 2016 (14 February). Vol. 30:327.

Introduction
Helicobacter pylori infection has a worldwide prevalence and causes some serious damages to human health. The infection increases the probability of gastric and duodenal ulcers, Mucosa Associated Lymphoid Tissue (MALT), lymphoma and gastric cancer (1-3). The prevalence rate varies worldwide ranging from 40% in developed countries to 80% in developing countries (4). Helicobacter pylori infection occurs during childhood and may cause gastritis,
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typically without symptoms (5). According to the global statistics, particularly the World Health Organization’s, the global burden of diseases attributable to H. pylori infection, which consist of a wide range of digestive system diseases including gastritis, gastric cancer, gastrointestinal bleeding, gastric and duodenal ulcers and indigestion are growing; and evidence shows that gastric cancer is the second leading cause of human mortality (6,7). According to the Iranian statistics, the prevalence of Helicobacter pylori infection in the northern and southern Iran has been more than 80%, and a significant part of the infected population faced subsequent diseases such as duodenal ulcer and gastric cancer (8,9). In this regard, the lack of infection symptoms, especially through the childhood, is the main concern, which causes late start of the treatment process (10). Attributing the probability of getting the infection into the economic and social, genetic, ethnic and demographic factors is considered as another point of concern (11).

The national and international economic consequences of Helicobacter pylori are remarkable. One study showed the cost of illness per person per six-months for patients with gastro-esophageal reflux diseases (GERD) and dyspepsia alone was around PPP$ 111(320,609 I.R. Rials) – PPP, purchasing power parity- and PPP$ 120 (345,935 I.R. Rials), respectively in 18,180 residents of Tehran from May 2006 to December 2007(12). Also, the researchers in another study estimated the direct costs of disease for GERD, dyspepsia and their overlap to be PPP$ 97.7 and PPP$ 101.3, respectively. The indirect costs of diseases per patient was PPP$ 13.7, PPP$ 12.1, and PPP$ 32.7, for GERD, dyspepsia and their overlap, respectively (13). There are different but considerable evidence about the economic burden of Helicobacter pylori infection in other countries. In Malaysia (2010), the cost of dyspepsia per 1,000 population per year was estimated at US$ 14,816.1 and US$ 59,282.2 in rural and urban populations, respectively (14). The total cost of peptic ulcer disease and gastro-esophageal disease was US$ 424 million or US$ 63 per adult. The share of direct cost is about 61% from the total cost (15).

Given the role and importance of timely and accurate diagnosis of infection in the treatment and control of digestive system diseases and disorders, the use of safe, accurate and optimal cost-effective diagnostic methods is of a great necessity. Diagnostic tests in two forms of invasive and noninvasive were introduced and used to diagnose Helicobacter infection. Invasive tests include the rapid urease test and histological examination of gastric mucosal tissue and cell culture. On the other hand, noninvasive tests include serology (such as immunoglobulin G and A; antibodies against cell surface antigens), carbon urea breath test and faecal antigen tests (16). In the meantime, the emphasis on invasive or noninvasive methods depends on some factors such as cost, accuracy and ease of use. Among the above mentioned diagnostic tests, carbon urea breath test, due to its noninvasive nature and ease of use, has been addressed in several studies and many issues have been raised about its application (5).

The high prevalence of Helicobacter pylori between Iranian population and the lack of decision-making evidence led us to conduct the current study. This study encompasses descriptive and analytical implications about the significance of effective management of Helicobacter pylori infection for Iranian health policy makers.

Given the significant importance of timely diagnosis of the mentioned infection and its impact on avoiding the imposition of significant costs on the health systems, this study aimed to measure and compare cost-effectiveness and cost-utility ratios of carbon 13 urea breath test, serology and histology among the Iranian adult population using Markov model.

Methods

Economic Evaluation Type: This was a cost- effectiveness and cost- utility analysis
that calculated and compared the cost per symptoms free cases and cost per QALYs for treatment regimens of *Helicobacter pylori* infection.

**Type of Interventions:** There are invasive and non-invasive diagnostic tests to detect the *Helicobacter pylori*. In addition, there are different therapeutic regimes to eradicate it. The diagnostic techniques are used as supplementary treatments for *Helicobacter pylori* infection as well. Hence, according to the literature (16-19), in this study, the economic evaluation compared strategies including both diagnostic and therapeutic methods.

We considered four therapeutic strategies for managing the *Helicobacter pylori*. The first three, called the test-and-treat regime are as follows: Proton Pomp Inhibitor based triple treatment after infection detected by each of 13 CUBT, serology, and histology tests.

**Study Population and Setting:** We performed the calculations and comparisons on 100,000 hypothetical Iranian adult population with uninvestigated dyspepsia who had not used Non-Steroidal Anti-Inflammatory Drugs (NSAID) and had no symptoms of other diseases.

**Dates and Sources of Data:** The data on the effectiveness and quality of life were obtained from previous studies published during the recent 10 years. Data about costs were collected through a field study in Tehran from April 2014 to June 2014. Moreover, for sensitivity analysis, the cost data in Iran’s health services fee schedule (2014) was used alongside the field study.

**Modeling and Assumptions:** A Markov model with a health services provider’s perspective and one-year time horizon was used. The model encompassed two cycles: In the first cycle, to detect the probable infection, all those suspected to have *Helicobacter pylori* infection were asked to undergo one of the three diagnostic tests (13 CUBT, serology or histology). If the test result was negative, the participants went to the first branch of the model and got the gastric acid anti-secretory regimen. In this regimen, each individual takes two pantoprazole 40 mg tablets per day for four weeks. After eight weeks, the individual is tested for *Helicobacter pylori* symptoms free status. If the symptoms are relieved, the individual reaches their mission state, but if the symptoms are not relieved, she/he falls in the recurrence state. All individuals in the recurrence state receive long-term medical supervision.

If the diagnostic test result was positive, the individual went on test-and-treat regime that contained a PPI based triple treatment. Here, the three diagnostic tests, with respect to their sensitivity and specificity and the number of patients were different in each treatment regimen. There are different numbers of detected patients with respect to the diagnostic test. Therefore, we faced three sub-strategies: (i) If 13 CUBT was used as the first diagnostic test, the sub-strategy would then be called UBT triple treatment; (ii) If serology was used as the first diagnostic test, the sub-strategy would then be called serology triple treatment; and (iii) if histology was the first diagnostic test, the sub-strategy would then be called histology triple treatment.

In this regimen, the patient takes two omeprazole 20 mg, four amoxicillin 500 mg and two clarithromycin 250 mg daily for four weeks. Also, 12 weeks after finishing the initial triple treatment, endoscopy was used to confirm the eradication, and symptoms-free state (remission state). Therefore, if the result was positive, the individual would be in the recurrence state and would need a long term care.

These strategies and the medications used to treat infection have been selected based on the international and national guidelines (20, 21) and availability of the drugs in the pharmacopoeia and pharmaceutical market in Iran. For example, according to the new guidelines, amoxicillin 1000 mg is one of the drugs used in triple therapy, but due to the lack of compliance with the conditions prescribed by physicians in the country, inevitably, its equivalent, two capsules of amoxicillin 500 mg were used. This was
the case for proton pump inhibitors. Although the derivatives of the two medicines, benzimidazole and imidazopyridine, are the main medicines as proton pump inhibitors in the global market, pantoprazole 40 mg and/or omeprazole 20 mg are used in Iran. The explanation of each strategy has been provided as follows:

The model assumptions have been presented in Table 1.

**Outcomes**

The main outcomes were as follows: The estimated symptoms-free cases, and quality adjusted life years (QALYs) at the end of two Markov cycles. The symptom-free cases were estimated through the multiplying the transition probabilities between the two Markov cycles by supposed infected individuals entered to each Markov state. The QALYs were calculated through multiplying the weights of utility-extracted from relevant studies- by the number of individual in each Markov state.

**Costing:** Although there is a market price for any resource utilized to diagnose and treat the Helicobacter pylori, many experts believe that the prices cannot reflect the real costs, Therefore, all related costs were calculated by the researchers independently. In this study, the activity-based costing method was used to estimate the cost of each diagnostic procedure and subsequently the cost of two treatment strategies. The data about performing the diagnostic tests have been collected through a field study in

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two private laboratories in Tehran. The medicines price was obtained from Iranian Ministry of Health and Social Security Organization. This has been done through the following steps:

1. Identification of the building process and activities of each strategy: Two strategies have been considered for Helicobacter pylori infection management: The proton-pump inhibitor-based triple therapy, and the gastric acid anti-secretory therapy, each of which includes some processes and activities. As mentioned earlier, both strategies begin with invasive or non-invasive diagnostic tests and then the therapeutic phase is managed with respect to the positive or negative detection of Helicobacter pylori infection. If the result of the test is positive the infected person pays appropriate visits to the doctor, consultations and medical procedures. The therapeutic plan includes physician’s examination and consultations, prescribing the drugs and finally investigating the eradication of infection. This process needs four physician’s visits as activities.

2. Classification of each activity according to the cost hierarchy: The output of the first step is called activity center. In this study, there are three main activity costing centers: Detection activities, therapeutic activities and follow-up activities. The 13 C-UBT, serology and histology are three routine tests performed in laboratory setting. 13 C-UBT is a simple and fast test (about 15-40 minutes), usually done by a laboratory technician, but the results are interpreted by a specialist. However, the histology and serology tests are more time consuming and need more medical equipment. The therapeutic plan is the second important activity center that includes the PPI-based triple and anti-secretory regimens. The physician’s examinations, consultations, and prescriptions are the main activities in this phase. The follow up phase is the final activity center that includes a physician’s examination and a diagnostic test to confirm the eradication of the infection (usually a biopsy-based test).

3. Identification and accumulation of the total costs of each activity: Each activity has been broken down into two components of the consumed time, and motion or effort of production resource. The histology test in the diagnostic phase contains the consumption of a share of each resource. The Tissue Processor, Tissue Flat, light microscope, microtome and paraffin dispenser are the main equipment in the Helicobacter pylori infection detection, but they are used to perform many microbiological tests. In this case, we divided the allocated time to Helicobacter pylori infection detection to all the activity time of equipment during the past year. The cost of manpower has been calculated through the time that was allocated to Helicobacter pylori infection by histology. This includes the allocated time by technicians, administrative employees and pathologists. With respect to the annual wages or salaries paid to each of them and the number of Helicobacter pylori infection tests that are performed, the allocated times has been calculated and then the unit cost of the manpower was estimated. The space cost has been computed through multiplying the occupied area of histology test setting (the equipment and manpower) by the monetary value of a commercial unit in a central district in Tehran.

The consumed energy costs were calculated with respect to the activity time of the histology equipment and its proportion from the total time of activity in the past year. This principle has been performed for the cost of other Helicobacter pylori infection tests and the management phases.

4. Identification of the most appropriate cost drivers for each activity: As mentioned in the previous step, it is of great importance to allocate an appropriated measurement unit to each activity. When we use resource-based costing, one of the most important steps is to determine the amount of consumption of resources (manpower, equipment, space, energy, supplies and materials). For example, in the diagnostic phase, the technician and
physician’s cost, is measured by the needed time to perform each test, or the energy cost is calculated through the KW per hour.

5. Calculation of the unit costs: As the final step, the unit cost of each of the resources is calculated through dividing the total cost to the total amount of the produced services. The histology unit cost was calculated through dividing the total costs related to manpower, equipment, material and supplies, space, administrative affairs etc., to the total accomplished tests.

Table 2 demonstrates the costing components of each diagnostic test. The resource used the market prices. Data were collected from the provider’s self-reported costs and his/her bills and the Iranian Ministry of Health and Social Security Organization.

**Sensitivity Analysis:** To investigate the effects of the uncertainty of relevant input variables (the prevalence of *Helicobacter pylori* infection, the sensitivity and specificity of diagnostic tests, the probability transitions between health state, and the costs of diagnostic tests and therapeutics...
regimens), a probabilistic sensitivity analysis was conducted. The probability distributions were specified for the mentioned variables, and the Monte Carlo simulation was performed for 1,000 iterate points. The cost-effectiveness plane was drawn for considered strategies.

It should be noted that all calculations of the costs, cost-effectiveness and cost-utility ratios as well as drawing the Markov model were done using Microsoft Excel 2010.

**Results**

The results of this study are demonstrated in two tables and five graphs. The other graphs on the cost per QALYs are presented in the appendix. Table 3 presents the unit cost of each strategy. The histology based triple treatment regimen was the most expensive, and the serology based anti-secretory regimens was the least expensive (Table 3).

Table 4 displays the cost per symptoms free results. The results indicated that the PPI based triple treatment, when serology was the first diagnostic test, was at the lowest amount. This result was also true about the cost per QALY ratio as well. Also, in anti-secretory regimens, if serology were used as the first diagnostic test, the cost per symptoms free and cost per QALY would have been at the lowest amounts compared to other strategies.

Figure 2 shows the graphical results of

| Strategies | Description | Incremental Cost** (I.R.I. Rials) | Incremental Effectiveness | Incremental QALYs | Cost per Symptoms free (I.R.I. Rials) | Cost per QALYs Gained in Population Allotted to Each Regimens (I.R.I. Rials) |
|------------|-------------|----------------------------------|--------------------------|------------------|----------------------------------------|--------------------------------------------------------------------------|
| PPI based Triple Therapy | Histology as first diagnostic test | 2.7 | 62582 | 45821 | 291736 | 339226 |
| | Serology as first diagnostic test | 3.3 | 25749 | | 1492103 |
| | 13C-UBT as first diagnostic test | 4 | 20521 | | 955698 |
| Antisecretory | Histology as first diagnostic test | 4.4 | 25871 | | 444512 |

Notes: *Comparators have been sorted based on the effectiveness -from the lowest to the highest. ** The figures should be multiplied by $\times 10^{11}$. Also, all of them were rounded.
Table 2, indicating that in triple treatment regimen, serology based strategy has clear dominancy to 13 CUBT strategy in both aspects of cost per symptoms free and cost per QALY. In addition, in anti-secretory treatment regimen, the serology-based strategy was dominant to histology-based strategy.

Costs: The unit costs of each strategy including both diagnostic and therapeutic phases are displayed in Table 3.

Table 3: Unit Costs of Each Helicobacter Pylori Diagnosis and Therapeutic Regimen

Cost- effectiveness Results: The results of the calculations of cost-effectiveness and cost-utility of the four mentioned strategies are provided in Table 4.

The cost-effectiveness plane of symptoms free cases are shown in Figure 2, and the information on the cost per QALYs is presented in the appendix.

Sensitivity Analysis: The results of the probabilistic sensitivity analysis through the Monte Carlo simulation are presented in cost-effectiveness planes in Figures 3 to 6, separately. The sensitivity analysis results for costs per QALYs are shown in the appendix.

![Fig. 2. Helicobacter pylori Symptoms-Free of Alternative Strategies at the End of the Cycles](image1)

![Fig. 3. The Scatter Plane of Symptoms-free Cases in Triple Treatment (13CUBT as first Diagnostic test vs. Serology)](image2)
The Monte Carlo simulation result has been presented in Figure 3.

The scatter plane of symptoms-free cases in triple treatment strategy when serology was used as the first diagnostic test vs. histology is shown in Figure 4.

The scatter plane of symptoms-free cases in anti-secretory treatment when serology was used as the first diagnostic test against UBT is presented in Figure 5.
Finally, the scatter planes of symptoms-free cases in antisecretory treatment when serology was used as the first diagnostic test against the serology is shown in Figure 6.

Discussion
Economic considerations are among the main dimensions when evaluating any health method or technology. With regards to the carbon-13 urea breath method, the results of this study showed that the unit cost is 1,939,740 Rials (US$ 65.42). If this method is used as the first diagnostic method of Helicobacter pylori infection, its unit cost in the triple therapy strategy would be 8,829,740 Rials (US $298) per patient, and in the gastric acid antisecretory therapy strategy- empirical strategy it equals to 1,281,000 Rials (US $43) per patient. On the other hand, if the serology method is used as the first diagnostic method of Helicobacter pylori infection, its unit cost - all three types of immunoglobulin= equals to 197,430 Rials (US$ 6.7); if the triple therapy is used for the patient, its unit cost equals to 6,748,320 (US$ 228); and in the gastric acid antisecretory therapy strategy, its unit cost would be 672,960 Rials (US$ 23). With regards to the histology method, its unit cost equals to 2,569,940 Rials (US$ 86.7); and if this diagnostic method is used in the triple therapy strategy, its unit cost would be 9,278,050 Rials (US$ 313); and in the gastric acid antisecretory therapy strategy, the unit cost equals to 3,853,000 Rials (US$ 130).

The cost per symptoms-free cases when the 13 CUBT was used as the first diagnostic test against serology was 1,283,200 Rials per symptoms-free cases and 1,492,103 Rials cost per QALYs in triple treatment strategy. Furthermore, the cost per symptoms free cases when serology was used as the first diagnostic test against histology was 291,736 and 339,226 Rials cost per QALYs. In antisecretory strategy, when histology was used as the first diagnostic test against the UBT, the cost per symptoms free was 793,234 and 955,698 Rials per QALYs. Finally, in this strategy, when serology was used as the first diagnostic histology test, the cost per symptoms-free cases was 368,947 Rials and 444,512 Rials per QALYs.

The sensitivity analysis through the Monte Carlo approach with 95% confidence interval on the main key outcome variables (the differences between costs, symptoms-free as the first outcome, QALYs, cost per symptoms-free and cost per QALYs) showed a consistency in our results. This was obvious about the triple treatment alternatives. In all of the strategies, the differences in costs and outcomes (symptoms free number or QALYs) had a relative smooth (linear) pattern. Nonetheless, a difference could be observed in antisecretory strategy when serology was used as the first diagnostic test against histology.

According to the calculations of the carbon-13 urea breath method, the high unit cost of the carbon-13 urea breath method, compared to the serology method, is nearly 10 times more expensive than the serology method. Moreover, the lack of significant difference in the effectiveness of the two methods (according to the literature review, the differences between the sensitivity of the carbon-13 urea breath method and the serology method was only 0.05) suggests no specific dominancy of the carbon-13 urea breath method over the serology method at high levels of the prevalence of the Helicobacter pylori infection. On the other hand, with regards to the histology method, the carbon-13 urea breath method has a comparative advantage in terms of the cost per symptoms-free and QALYs, particularly in the gastric acid antisecretory therapy strategy, owing to the low cost difference (the histology method is about 1.3 times more expensive than the carbon-13 urea breath method), and the approximate equality in the effectiveness of the two mentioned diagnostic methods.

Results of a study conducted in Canada reveals no superiority between the serology method and the carbon-13 urea breath method in terms of cost-effectiveness (19).
Although, it is important that the carbon-13 urea breath is more expensive, it is remarkably effective and can reduce the endoscopy referral burden. However, in sum, under the conditions of assumed parameters in the decision making model adopted by researchers of the current study, the carbon-13 urea breath method seems to be more cost-effective than the serology method. In general, the study concluded that the serology method is more appealing for patients with uninvestigated dyspepsia and at a low risk level.

A study was also conducted in Spain which aimed to evaluate the economic aspects of the general strategies including test- and treat and a treatment strategy without test (35). The authors concluded that overall, the treatment strategy was better than the test-treatment strategy in terms of cost-effectiveness. Furthermore, among the used test-treatment methods in the mentioned strategy, the serology-based method was the most cost-effective followed by the urease test and carbon-13 urea breath methods. In the meantime, the carbon-13 urea breath method was more cost-effective than the cell culture and histology methods.

In another study conducted in Canada, the researchers concluded that the test-treatment strategy based on carbon-13 urea breath method has been more cost-effective than the other alternatives including endoscopy and serology methods. While the diagnostic effectiveness of this test was more than the other two, it was the most expensive method, and applying it to detect Helicobacter pylori infection at the primary level should be based on its use as the optimal method of detection (36).

**Conclusion**

With respect to the existing prevalence of Helicobacter pylori infection in Iran, owing to the high price of the carbon-13 urea breath method, and lack of significant cost-effectiveness and cost utility superiority over the serology and histology, we recommend avoiding its application in large scale and for large population groups. However if prescribed, given the significant safety and diagnostic effectiveness, carbon-13 urea breath method should be used only for specific age groups, particularly children, and its use for older age groups does not seem cost-effective. In case that the prevalence of the Helicobacter pylori infection in Iran increases to a threshold of 93%, the use of the carbon-13 urea breath method may be cost-effective.

**Limitations of the Study**

Lack of valid data extracted from the related studies about the probability of symptoms recurrence in antisecretory strategy and the quality of life gained in PPI based triple treatment strategy resulted in some restrictions in conducting the sensitivity analysis. Nevertheless, it seems that these two parameters did not have much effect on our main results. The gastric cancer was one the most important outcomes of Helicobacter pylori infection, but was not investigated in our study. Thus, we recommend an economic evaluation considering gastric cancer in the future studies.

**Acknowledgement**

The author would like to thank Dr. Shahriar Khaghani for his valuable comments.

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Appendix

Fig. 1. *Helicobacter pylori* QALYs of the Alternative Strategies at the End of Cycles

Fig. 2. The Scatter Plane of QALYs in Triple Treatment (13CUBT as the first Diagnostic Test against Serology)

Figure 3: The Scatter Plane of QALYs in Triple Treatment (serology as the first Diagnostic test vs. Histology)
Fig. 4. The Scatter Plane of QALYs in Antisecretory Treatment (histology as first diagnostic test vs. UBT)

Fig. 5. The Scatter Plane of QALYs in Antisecretory Treatment (serology as first diagnostic test vs. histology)