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Abstract: INTRODUCTION: *Helicobacter pylori* infection (*H pylori*-I) affects more than half of the global population and consists an important burden to public health and healthcare expenditures, by contributing to many diseases' pathogenesis. AIM: This study aimed to evaluate the current nonbismuth quadruple eradication regimens in a high antibiotic resistance area, such as Greece, concerning their cost-effectiveness, especially during financial crisis period. MATERIALS AND METHODS: Eight hundred and nine patients who received eradication treatment against *H pylori*-I were included to evaluate five different regimens, using amoxicillin, clarithromycin, and metronidazole as antibiotics and one proton-pump inhibitor, based on their current eradication rates. Regimes compared 10-day concomitant use of (a) pantoprazole or (b) esomeprazole; 10-day sequential use of (c) pantoprazole or (d) esomeprazole; and 14-day hybrid using esomeprazole. Cost-effectiveness analysis ratio (CEAR) and incremental cost-effectiveness ratios were calculated taking into account all direct costs and cases who needed second-line treatment. Additionally, sensitivity analysis was performed to predict all potential combinations. RESULTS: Ten-day concomitant regimen with esomeprazole was characterized by the lowest CEAR (179.17€) followed by the same regimen using pantoprazole (183.27€). Hybrid regimen, although equivalent in eradication rates, was found to have higher CEAR (187.42€), whereas sequential regimens were not cost-effective (CEAR: 204.12€ and 216.02€ respectively). DISCUSSION: This is the first study evaluating the cost-effectiveness of *H pylori*-I treatment regimens in a high clarithromycin-resistance (26.5%) European area, suggesting the 10-day concomitant regimen with generics using esomeprazole 40 mg as the most appropriate one. National and regional guidelines should include cost-effectiveness in their statements, and further studies are required to clarify the necessity of a wide "test and treat" policy for *H pylori*-I.

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***Helicobacter pylori* eradication regimens in an antibiotic high-resistance European area: a cost-effectiveness analysis**

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Running Head: Cost-effectiveness of *Hp* eradication regimens

Abstract

Introduction: *Helicobacter pylori* infection (*Hp-I*) affects more than the half of the global population and consists an important burden to public health and health care expenditures, by contributing to many diseases' pathogenesis.

Aim: This study aimed to evaluate the current non-bismuth quadruple eradication regimens in a high antibiotic resistance area, such as Greece, concerning their cost-effectiveness, especially during financial crisis period.

Materials and Methods: Eight hundred and nine patients who received eradication treatment against *Hp-I* were included to evaluate five different regimens, using amoxicillin, clarithromycin and metronidazole as antibiotics and one proton pump inhibitor, based on their current eradication rates. Regimes compared: 10-day concomitant use of 1) pantoprazole or 2) esomeprazole; 10-day sequential use of 3) pantoprazole or 4) esomeprazole; and 14-day hybrid using esomeprazole. Cost-effectiveness (CEAR) and incremental cost-effectiveness ratios were calculated taking into account all direct costs and cases who needed second-line treatment. Additionally, sensitivity analysis was performed to predict all potential combinations.

Results: 10-day concomitant regimen with esomeprazole was characterized by the lowest CEAR (179,17€) followed by the same regimen using pantoprazole (183,27€). Hybrid regimen, although equivalent in eradication rates, was found to have higher CEAR (187,42 €), whereas sequential regimens were not cost-effective (CEAR: 204,12€ and 216,02€ respectively).

Discussion: This is the first study evaluating the cost-effectiveness of *Hp-I* treatment regimens in a high clarithromycin-resistance ($\approx 26.5\%$) European area, suggesting the 10-day concomitant regimen with generics using esomeprazole 40mg as the most

appropriate one. National and regional guidelines should include cost-effectiveness in their statements and further studies are required to clarify the necessity of a wide “test and treat” policy for *Hp*-I.

Conflict of interest

None declared

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Keywords

Helicobacter pylori, *Hp* infection, treatment cost-effectiveness, eradication regimens

Abbreviations

CEAR; cost-effectiveness analysis ratio, ER; eradication rates *Hp*; *Helicobacter pylori*, *Hp*-I; *Hp* infection, ICER; incremental cost-effectiveness ratio, PP; per protocol, PPI; proton-pump inhibitor, UBT; ¹³C-urea breath test

Introduction

Helicobacter Pylori (*Hp*) affects around 52,1% to 58% individuals globally and is highly prevalent in Greece as well. The incidence increases particularly in southern European regions due to immigration¹.

A broad spectrum of *Hp*-related gastric and extragastric disorders has been described. Specifically, peptic ulcer disease, gastritis, gastric atrophy, gastric cancer, gastric mucosa-associated lymphoid tissue lymphoma, idiopathic thrombocytopenic purpura

or iron-deficiency anemia are conditions requiring *Hp* eradication regimens². Examples of *Hp* infection (*Hp-I*) related extragastric disorders, include colorectal cancer and esophageal adenocarcinoma at least in certain subpopulations, metabolic syndrome, Alzheimer's disease or glaucoma, representing a significant burden to public health²⁻⁸.

Additionally, *Hp* eradication treatment is becoming more challenging due to its increasing antimicrobial resistance⁹, which induces frequent adjustments of eradication regimens, by adding more drugs, especially in regions where bismuth regimens are not available, such as in Greece^{2,10,11}. This “add-on” strategy not only increases the total eradication costs, but also perpetuates ultimately the vicious circle of resistance and treatment¹².

Financial crisis has been established in Europe during the last decade, with Greece being one of the most recognizable examples of the resultant aftermaths. Before the financial crisis, medication prices in Greece were among the highest in Europe¹³, whereas from 2009 to 2016, the health care expenditure was reduced to around 40% in Greek Health Care System as presented by Eurostat¹⁴. Cost-effectiveness analysis is an important tool to guide public policy makers in decisions of resource allocation and by crisis' onset a plethora of them have been performed in Greece for various medical conditions, thus assisting to this direction and emphasizing opportunity costs. The economic hardships in our country have, also, disturbed the dynamics of infectious diseases¹⁵. Regarding *Hp-I*, which belongs to the most complex and quite expensive community-related infections to manage, there are no updated studies evaluating the cost-effectiveness of currently suggested quadruple eradication regimes, especially in areas with high-resistance to antibiotics². Therefore, we aimed to elucidate this parameter based on the latest guidelines for *Hp* eradication^{2,9}, in order to propose the most appropriate eradication treatment for regions with high resistance to

clarithromycin, such as Greece with respect to the cost and efficacy of suggested regimens and proton-pump inhibitor (PPIs) dependent variants.

Materials and Methods

Patient collection

For this study, being a second parallel multicenter project, we collected data from three recent, prospective studies of our colleagues that were conducted from September 2012 to March 2016, concerning successful eradication rates of the three most commonly used eradication regimens in Greece, according to the current guidelines^{16–18}; 10-day concomitant, 10-day sequential and 14-day hybrid regimens characterized by different combination of amoxicillin 1g, clarithromycin 500mg and metronidazole 500mg as antibiotics plus PPIs were studied. Administration of levofloxacin 500mg once daily, amoxicillin 1g and esomeprazole 40mg twice daily for fourteen days was considered as the second-line rescue treatment. Figure 1 summarizes the aforementioned regimens.

Adult participants between 18 and 80 years old with *Hp*-I related dyspepsia, iron deficiency anemia or peptic ulcer disease without previous *Hp* eradication treatment constituted the patients' reservoir. Those with contraindications to studies' medication, severe comorbidities and serious systemic disease, history of esophageal or gastric surgery or gastric malignancies, recent administration of antibiotics, PPIs, bismuth preparations or non-steroid anti-inflammatory drugs ingestion and pregnant or lactating females were excluded^{16–18}. Eight hundred and nine consecutive patients, divided to five therapy-specific subgroups, completed the treatment originally allocated, and therefore were totally included for per protocol (PP) analysis. Two groups compared the eradication rates of 10-day concomitant versus 10-day sequential regimens using

pantoprazole; the same protocol was introduced by using esomeprazole for two more groups. The last patient group received hybrid regimen.

All patients gave written informed consent before enrollment, and the study protocol was approved by the medical Ethics Committee of the hospitals in which the study was conducted^{16–18}. All participants underwent upper gastrointestinal endoscopy. Gastric biopsies specimens were obtained for the presence of *Hp*-I and tested by rapid urease slide test (CLO test) and by Giemsa staining; positive CLO test (Kimberly-Clark, Utah, USA) (with reported 98% sensitivity and 97% specificity¹⁹) was confirmed by the presence of *Hp* bacteria histologically in all participants (sensitivity: 80–95% and specificity: 99–100%)^{20,21}. The treatment results were evaluated by ¹³C-urea breath test (UBT) (Helicobacter Test INFAI®, GmbH, Cologne, Germany) at least four to six weeks after treatment (sensitivity and specificity >95.7%)²⁰. The main pillars of these studies are summarized in Figure 2.

Cost-effectiveness analysis

A cost-effectiveness analysis and comparison of the most commonly used regimens were conducted, to describe the cost per unit health improvement of each treatment strategy, using a decision analytical tree to calculate the overall cost of each regimen (Figure 3). In this study, the eradication rates of each intervention were considered as target units. Each intervention was assessed according to this outcome, thus providing results about the technical efficiency of each regimen²².

Direct pharmaceutical costs, in euros, for one attempt “out-patient” *Hp* eradication treatment both for prototypes and generics drugs were collected by our group, according to the most recent retail price configuration in June 2018²³. As second line rescue

treatment was considered the 14-day levofloxacin-based regimen (Figure 1) containing esomeprazole 40 mg as the prescribed PPI². The overall cost of each regimen choice was calculated by a formula including the aforementioned regimens' retail costs using the cheapest generics as the most affordable choice, costs of unsuccessful eradications and other diagnostic costs, as summarized in Table 1, and presented below:

$$\text{Total Cost} = \text{ER} \times (\text{cost}^{1.\text{line}} + \text{UBT} + \text{Endoscopy}^{\text{CLO}} + \text{Histology}) + (1 - \text{ER}) \times (\text{cost}^{1.\text{line}} + 2 \times \text{UBT} + \text{Endoscopy}^{\text{CLO}} + \text{Histology} + \text{cost}^{2.\text{line}}),$$

with ER: eradication rate; $\text{cost}^{1.\text{line}/2.\text{line}}$: cost of first line and second line eradication treatment respectively; $\text{Endoscopy}^{\text{CLO}}$: cost of an Esophagogastroduodenoscopy including CLO-test; Histology: cost of pathological examination and Giemsa stain.

Unit costs supplied by the Greek National Organization of Health Care benefits Provision (Table 1). The study was performed with a National health care perspective.

Cost-effectiveness was evaluated by dividing the total costs per 100 treated individuals to the eradication rate of *Hp* for every regimen. The incremental cost-effectiveness ratio (ICER) was performed to evaluate a regimen's choice to a less effective but also more affordable one and to estimate additional costs, by the following mathematical equation:

$$\text{ICER} = \frac{\text{Cost}_{\text{regimen1}} - \text{Cost}_{\text{regimen2}}}{\text{Eradicated } Hp \text{ case}_{\text{Sregimen1}} - \text{Eradicated } Hp \text{ case}_{\text{Sregimen2}}}$$

with $\text{Cost}_{\text{regimen}}$: Total Cost per 100 *Hp* cases treated with regimen 1 and 2 respectively and $\text{Eradicated } Hp \text{ case}_{\text{Sregimen}}$: Eradicated *Hp* cases per 100 treated with regimen 1 and 2 respectively.

Sensitivity Analysis

Sensitivity analysis using various effectiveness values per regimen and PPIs combinations was performed to estimate a potential uncertainty parameter in our decision tree model. A best-/worst case analysis, included six different effectiveness values and their related costs. The lowest acceptable effectiveness²⁴ (85%), as well as eradication rates of 90% and 95% were assigned with the corresponding cost.

Results

Regarding *Hp* eradication regimens in the three aforementioned studies, the 10-day concomitant regimens using esomeprazole 40mg and pantoprazole 40mg yielded 93.4% and 90.6% eradication PP success rates, respectively. The eradication rates of the 10-day sequential regimens were 82.8% and 78.1%, respectively^{17,18}. The 14-day hybrid yielded a 90.2%^{17,18}. The 14-day hybrid yielded 90.2% eradication rate. *Hp* resistance to clarithromycin was confirmed to be high ($\approx 26.5\%$)^{16,17}, whereas dual resistance concerning the combination of both clarithromycin and metronidazole was acceptable ($<9\%$)¹⁶.

Hp eradication decision tree (Figure 3) maps the components of the total direct costs of each studied regimen per patient to treat a hundred patients, as a result of the financial burden of both successful eradication and failure. Table 2 summarizes the total cost per regimen for 100 patients as well as the associated CEARs. Concomitant regimens using esomeprazole marginally yielded the favorable CEAR over pantoprazole regimens (179,17€ and 183,27€ respectively), whereas hybrid regimens with esomeprazole, although equivalent in eradication rates, yielded higher CEAR (187,42 €). The 14-day sequential regimens yielded higher CEARs (216,02€ and 204,11€ for

pantoprazole and esomeprazole based sequential regimens respectively), owing to the low quotient's denominator.

The ICER analysis (Table 3) revealed that additional costs per patient for prescribing concomitant regimen in one additional patient using esomeprazole 40mg instead of pantoprazole 40mg were 46,48€. Furthermore, a negligible extra burden of 0,62 € per patient was revealed after ICER analysis for hybrid regimen over sequential regimen respectively. In cases of evident domination of a regimen over another, regarding both eradication rates and cost, ICERs were not calculated; for example, 10-day concomitant regimens yielded higher eradication rates than 14-day sequential ones plus consuming fewer expenses.

Sensitivity analysis was based on both original and generics fixed medication prices for all regimens differentiated by PPIs and resulted in the elaborate Table 4, which provides the estimated predictions of the CEAR for any possible combination of the recommended *Hp* eradication regimens in Greece, based on three acceptable success percentages (85%, 90% and 95%)²⁴. As expected, for each regimen the CEAR decreased as eradication rate increased and pantoprazole provided the most affordable choice in each regimen, signifying a uniform eradication rate per regimen.

Discussion

This first cost-effectiveness study, evaluating non-bismuth *Hp* eradication regimes and PPI variants according to the latest official guidelines^{2,9} in a high clarithromycin resistance area¹¹, showed the 10-day concomitant regimen using esomeprazole to be the most cost-effective. The study may serve as a landmark for treatment decision making not only nationally (in Greece), but also in other European areas with high

resistance to antibiotics. Furthermore, the results of our sensitivity analysis enhanced the reliability of our results, by quantifying the influence of each regimen's eradication rates on cost-effectiveness and provided a CEAR based tool to clinicians to decide about the most appropriate regimen depending on the national and regional eradication rates, with respect to the cost.

Nevertheless, this study had some limitations. ~~The most important limitation of the study was the retrospective design, which did not allow to evaluate parameters such as the time spent by the individuals for examinations or work productivity loss.~~ The retrospective design did not allow a random allocation of patients and they were allocated according to the treatment regimen. This was the most important limitation and did not allow the evaluation of further parameters such as the time spent by the individuals and productivity loss, thus depriving the potential societal perspective of the study. However, our data were collected prospectively and appeared to be the most recent concerning *Hp-I* in Greek population with eradication rates and *Hp* resistance to antibiotics being immutable the last years. Additionally, we did not perform a cost-utility or -benefit analysis, by recording differences in long-term health and financial benefits among *Hp* eradication regimens, as eradication itself is the main target in *Hp-I* related conditions. In this respect, 10-day concomitant regimen with esomeprazole, despite the elevated cost, was the most cost-effective, due to the highest eradication rate, **assuming that the decreased incidence of *Hp-I* would result in reduced *Hp-I* related complications.** ~~thereby spontaneously prejudging decreased incidence of *Hp-I* induced complications.~~ However, further studies are necessary to quantify this benefit. Additionally, we used a snapshot of drugs' market prices whereas fluctuations have not been predicted in this study. Nevertheless, alterations in pharmaceutical prices in Greece, especially during financial

crisis, are predominantly determined by horizontal governmental policies, affecting drug prices analogically. Although the difficulty of the direct extrapolation as well as the generalizability of our findings, given the inherent variability of pharmaceutical prices in different countries, our results provide an original guidance, at least for countries with high antibiotic resistance (either clarithromycin or/and metronidazole) and financial decline. Furthermore, we cannot confirm that all of our patients received generics, although it seems the most possible and reasonable scenario based on the point that the Greek National Health System obliges doctors to prescribe generics and more importantly the pharmacists to provide generics to any patient unless the patient decides to pay more for the prototype selection or owing to generics intolerance. Since there are no surveys comparing eradication rates between prototypes- and generics- based regimens, this issue is of great interest for further evaluation.

Our sensitivity analysis model included all of the current prices of available eradication regimens in Greece as baseline to predict all the CEAR upon future eradication rates change, presupposing stable drug prices. For example, a 10-day concomitant regimen using prototypes and omeprazole 20mg, assumed that eradicates *Hp* at a rate of 85%, will have a CEAR=218.4, being less cost-effective than 10-day concomitant regimen using prototypes and lansoprazole 30mg with 90% eradication rate (CEAR=203.9) (Table 4). These ratios could be compared to any other available eradication regimen, thus helping the clinicians to decide about the most appropriate cost-effective choice. Our results provide a modified “report-card” to grade *Hp* eradication based on CEAR, taking into account both regimens’ costs and local eradication rates, which seem to be necessary to manage *Hp*-I in areas with high clarithromycin resistance, like Greece ^{24,25}.

The findings showed that the 10-day esomeprazole based concomitant regimen was the most cost-effective one, thus spending 16734,86€ to treat one hundred patients.

Relative important calculations indicate that the mentioned estimated global prevalence of *Hp-I* is around 52,1% to 58%¹, corresponding to 5.635.285 and/or 6.273.446 Greek people respectively and the National Health System would spend 943.064.945€ to 1.049.861.188€ to treat all of them using the most cost-effective regimen with generics. According to the most recent (2016) official data presented by Eurostat, the total health care expenditures in Greece were 14.727.320.000 €, thus implying that 6.4-7.13% of this annual budget would have been disposed, if the half of the Greek population received the esomeprazole 10-day concomitant regimen¹⁴. **The population screening could be a once per birth cohort investment, since re-infections rates are low in adults.** Nevertheless, this percentage does not represent the real balance between benefit and cost of a wide *Hp-I* eradication; not only the costs of a broad screening program and potential adverse effects, such as direct complications or long-term increase of antibiotic resistance, but also the funds saved by *Hp-I* complications' prevention have not been calculated, something that could constitute an object of further survey. A recent comprehensive study, performed in a low *Hp* prevalence and low antibiotic resistance area, stated against cost-effectiveness of population *Hp* screening and pointed to population adherence as a real challenge²⁶.

Recent data indicate that the increasing resistance to clarithromycin and metronidazole, being triggered by the excessive antibiotic prescription^{11,27}, is the most determinant hindrance of *Hp* eradication treatment success **and the most important concern when considering population Hp screening**²⁸. In South Europe, which is coincidentally affected more dramatically by financial crisis, a higher resistance of *Hp* strains has been noticed compared to northern countries, and with respect to Maastricht V/Florence Consensus², regional *Hp-I* treatment guidelines have been developed, defined by these resistance rates^{29,30}. When bismuth containing regimens are either not available, as in

our country, or not a choice for any reason, some authors propose efforts to achieve resistance data, or otherwise to introduce concomitant personal regimens⁹. Elevating single and double resistance rates could gradually generate alternative eradication strategies, either by requiring all the necessary arrangements by authorities to ensure the disposal of bismuth containing regimens in Greece or by adopting a radically different approach. Such approach requires the establishment of routine *Hp* culture and antibiogram as the first step of a targeted therapy³¹. Alternatively a genotypic resistance-guided triple therapy based on a simple, commercially available, molecular assay³², could possibly achieve better eradication rates though increasing the overall management cost. Interestingly, a recent randomized controlled trial showed that susceptibility-based and empiric bismuth quadruple regimens offer equally excellent *Hp* eradication rates, thereby signifying a potential clinical introduction of these regimens depending on availability of susceptibility testing and/or a locally very efficient empiric regimens³³. All of the aforementioned strategies necessitate systematic evaluation to illuminate both regimens' effectiveness, but also their impact to Public Health expenditures.

A further novelty of our study focused on the comparison between eradication regimens differing in PPIs, by evaluating the ICERs of regimens using pantoprazole (1st generation PPIs) and esomeprazole (2nd generation PPIs). Both esomeprazole-based concomitant and sequential regimens were found to be more cost-effective strategies than the respective ones based on pantoprazole. Shimoyama et al³⁴, in an isolated study, suggested equivalent eradication rates between triple regimens differing in PPIs based on CYP2C19 polymorphisms, although these rates were already low probably resulted by *Hp* resistance to clarithromycin³⁴. On the other hand, a meta-analysis confirmed the

superiority of new generation PPIs and especially esomeprazole use in *Hp* eradication regimens³⁵.

In conclusion, this is the first study suggesting that the 10-day concomitant eradication regimen using generics and esomeprazole is the most appropriate choice in a high clarithromycin-resistance area, by evaluating its cost-effectiveness. Future studies, however difficult to perform, should include the cost-effectiveness analysis and the variables that affect cost-effectiveness, such as hospitality, medication, quality of life, adverse effects, working hours of medical staff, as well as savings resulted by *Hp* eradication – peptic ulcer disease cases, dyspepsia, use of PPI, gastric cancer- and last but not least cost of antibiotic resistance surveillance. Finally, under the notable economic burden of health care systems globally, national strategies and treatment guidelines should include similar studies in order to achieve better overall benefits for the national health care systems by evaluating and deciding the most suitable regimens against *Hp-I* according to regional eradication rates and drug prices.

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