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PHARMACOECONOMIC COMPARISON OF TREATMENTS FOR THE ERADICATION OF *HELICOBACTER PYLORI* IN ENUGU STATE, NIGERIA

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ABSTRACT

This study aimed at describing the cost-effectiveness of four regimen commonly employed in Enugu State, Nigeria for eradicating *Helicobacter pylori*. A decision analysis model was constructed to represent the strategies used in eradication of *H. pylori* in most practice setting in Enugu State. Each of the four strategies was hypothesized to have been administered to a cohort of 100 patients. Cost of medication was the only cost component included and were based on 2007 prices. Base estimates for eradication of *H. pylori* with omeprazole, clarithromycin and metronidazole (OCM), omeprazole, amoxicillin and metronidazole (OAM), and re-treatment with OCM were obtained from an earlier published study. The average cost-effectiveness ratio was determined. Incremental costs of the strategy with highest effectiveness in relation to other strategies were also calculated. The unit of comparison for evaluating cost-effectiveness was the number of years it would take for the cumulative future cost of treating a patient with relapse treatment, to equal the incremental cost of the most effective eradication therapy. The use of OAM in eradication of *H. pylori* in patients with duodenal ulcer and re-treating with OCM in patients that still shows dyspeptic symptoms is the most cost-effective option compared to the other three strategies.

Keywords: *Decision analysis; duodenal ulcer; cost-effectiveness; Helicobacter pylori.*

INTRODUCTION

Helicobacter pylorus is ubiquitous in Africa, with acquisition in childhood the rule[1]. It has been established that most patients with a duodenal ulcer and many with gastric ulcers are colonized with *H. pylori* [2,3]. As a result, many investigators have divided peptic ulcer disease into three etiologic groups based on pathophysiologic abnormalities and they include: (1) ulcers associated with *H. pylori* infection, (2) those caused by NSAID use, and (3) those with acid hypersecretion[4]. Patients who remain positive for *H. pylori* have a higher recurrence rate within the first year after healing compared with patients in whom eradication of *H. pylori* is achieved[5]. Over a 6- to 12-month period following initial ulcer healing, ulcer recurrence rates have been documented to be 85% in *H. pylori*-positive patients, but only 10% in *H. pylori*-negative patients[6]. Thus, *H. pylori* eradication therapy is recommended for all *H. pylori*-positive patients with confirmed gastric or duodenal ulcers, both patients presenting with first ulcers and those presenting with recurrence[7,8].

Monotherapy with antibiotics or with acid suppressants has not been optimal and thus, combination therapies consisting of antibiotics and suppressants (Proton pump inhibitors or H_2-receptor antagonists) have become the primary mainstays in the management of *H. pylori* positive ulcer patients[9]. However, different eradication regimens have dissimilar efficacy and wide variation in cost. Use of cost-effective regimen in the treatment of ulcer patients would result in resource savings for patients and would ensure efficient distribution of health resources. This study is an economic evaluation aimed at describing the cost-effectiveness of four eradication regimen commonly employed in Enugu, a state in South-Eastern Nigeria for eradicating *Helicobacter pylori*, using a hypothetical cohort of 100 patients.

METHODS

Decision analysis model

The model was constructed to represent the strategies used in eradication of *Helicobacter pylori* in most practice settings in Enugu State. Interview with five consultant gastroenterologists practicing in Enugu revealed that patients with clinical symptoms of ulcer are normally placed on *Helicobacter pylori* eradication regimen presumptively without any confirmatory test. Patients are monitored and if dyspeptic symptoms persist or reappear, they are given another course of eradication regimen or managed with H_2 receptor antagonist or proton pump inhibitors. *Helicobacter pylori* eradication regimen often made use of are omeprazole, clarithromycin, and metronidazole and omeprazole, amoxicillin, and metronidazole. Thus, a decision analysis model was constructed employing a simple decision tree to model four different strategies of eradicating *Helicobacter pylori* in patients with duodenal

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ulcer (Figure 1). The strategies used in the model included:

- *Strategy 1*: omeprazole (20mg) twice daily, amoxicillin (1g) twice daily, and metronidazole (400mg) twice daily, all for 7 days (OAM 7 days).
- *Strategy 2*: omeprazole (20mg) twice daily, clarithromycin (250mg) twice daily, and metronidazole (400mg) twice daily, all for 7 days (OCM 7 days).
- *Strategy 3*: Strategy 1 plus repeat therapy with omeprazole (20mg) twice daily, clarithromycin (250mg) twice daily, and metronidazole (400mg) twice daily, all for 7 days.
- *Strategy 4*: Strategy 2 plus repeat with omeprazole (20mg) twice daily, clarithromycin (250mg) twice daily, and metronidazole (400mg) twice daily, all for 7 days.

Patients in whom eradication treatment was unsuccessful would only have treatment for acid suppression with ranitidine (150mg), a H_2 receptor antagonist twice daily for 6 weeks, if they had recurrent ulcers that produced symptoms. Decision analysis was based on DATA software (version 3.5; Treeage Software, Williamstown, MA).

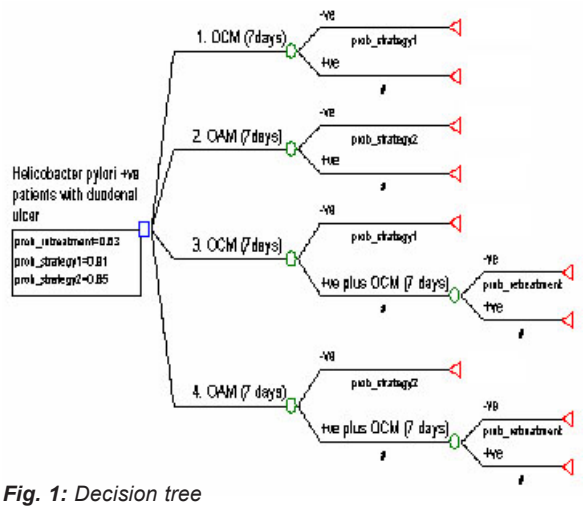

Fig. 1: *Decision tree*

prob_strategy1 = probability of eradication with OCM
prob_strategy2 = probability of eradication with OAM
prob_retreatment = probability of retreatment with OCM;
# = probability of eradication failure

Efficacy indicator

Base estimates for eradication of *Helicobacter pylori* with omeprazole, clarithromycin and metronidazole (OCM), omeprazole, amoxicillin and metronidazole (OAM), and re-treatment with OCM were obtained from an earlier published study[10]. In the study, estimates for the eradication of *H. pylori* with each regimen and the 95% confidence intervals were obtained by calculating the mean eradication rates of *Helicobacter pylori* from published non-randomised trials up to November 1995. For the OCM regimen there were 15 trials with a total of 1125 patients, with an overall eradication rate of 91%, and for the OAM regimen there were 4 trials with a total of 673 patients and an overall eradication rate of 85%. Estimates for the eradication of *H pylori* with a repeat therapy with omeprazole, clarithromycin, and metronidazole (OCM 7 days) after initial failure with either regimen were obtained by calculating the mean eradication rate of *H. pylori* using the regimen in patients who had failed eradication treatment from all trials up to October 1996[10]. Details of the efficacy estimates used in the study are shown in Table 1.

Table 1: *Efficacy and cost estimates of different strategies for eradication of H. pylori in Enugu State*

Variable	Eradication estimate	Range of estimate
†Eradication regimen (%)		
▪ Omeprazole, clarithromycin, metronidazole (7 days)	91	89-92
▪ Omeprazole, amoxicillin, metronidazole (7 days)	85	82-87
▪ Repeat omeprazole, clarithromycin, metronidazole (7 days)	63	55-71
*Cost for 100 patients		
▪ Omeprazole, clarithromycin, metronidazole (7 days)	N260,624	N194,530 - N273,686
▪ Omeprazole, amoxicillin, metronidazole (7 days)	₦67,424	₦36,610 – ₦93,086
▪ Strategy 1 plus repeat omeprazole, clarithromycin, metronidazole	N521,248	N389,060 - N547,372
▪ Strategy 2 plus repeat omeprazole, clarithromycin, metronidazole	₦328,048	₦231,140 – ₦366,772
▪ Relapse treatment with ranitidine (150mg) twice daily for 4 weeks	₦966	₦906 – ₦1092

†Estimates of eradication rates were obtained from Duggan et al, 1998
*Cost data were obtained from Central medical store, Enugu State
NB: US$1.00 is equivalent to ₦120.00

Cost data

Cost effectiveness was conducted from the perspective of the providers. Cost per patient assessment included the cost of omeprazole, clarithromycin and metronidazole, omeprazole, amoxicillin and metronidazole regimens, and the yearly cost of relapse treatment of duodenal ulcer disease with ranitidine 150mg twice daily for 4 weeks. Since indication for eradication of *H. pylori* is based on presumptive treatment and no confirmatory test conducted, only drug costs were used. Treatment for relapse was assumed to last for 6 weeks, and each patient that experienced failure with any of the eradication strategy would receive relapse treatment twice a year[11].

Cost effectiveness analysis

Hundred patients with duodenal ulcer, positive for *Helicobacter pylori* were assumed to be treated with each of the four strategies. The decision model explored the cost in eradicating *Helicobacter pylori* in these patients. For each successful *Helicobacter pylori* eradication, the average patient cost (ACER) was calculated with the formula below:

$$\text{ACER} \quad \frac{\text{Total cost for strayegy (x)}}{\text{Number of patients successfully treated with strategy (x)}} \qquad \text{(i)}$$

Incremental cost of the strategy with highest effectiveness was also calculated. Incremental cost represents the additional cost incurred for every patient that only the more effective strategy successfully treated. The incremental cost was determined by the formula below:

$$\text{ICER} \quad \frac{\text{Total cost of highest effictive strategy - Total cost of strategy (x)}}{\text{Number treated by highest effective strategy - Number treated by strategy (x)}} \qquad \text{(ii)}$$

Incremental cost was matched with the annual cost of treating a patient remaining positive for *Helicobacter pylori* with ranitidine 150mg twice daily for 4 weeks duration given once yearly. The unit of comparison for evaluating cost effectiveness was the number of years it would take for the cumulative future cost of treating a patient with relapse treatment, to equal the incremental cost of the most effective eradication therapy.

Sensitivity analysis

Sensitivity analysis was used to test the CEA results to parameter(s) alteration. Ranges of eradication rate estimates were used to perform one-way sensitivity analysis. The minimum and maximum cost of medications of the different eradication strategies were used in a multi-way sensitivity analysis to test the impact of price variation on the results obtained in the original analysis.

RESULTS

The differences in cost and efficacy outcome between the four *H. pylori* eradication strategies are described in Table 2. Considering only the cost of medication, using OAM to eradicate *H. pylori* will consume the least resources but also has the least efficacy (Strategy 2). Using OCM and repeating the same treatment in patients that had eradication failure (Strategy 3) would have the highest efficacy but also would consume the largest amount of resources. Eradication of *H. pylori* with OCM without repeat treatment (Strategy 1) has the second highest cost and efficacy. Using OAM plus repeat treatment with OCM for patients in whom eradication of *H. pylori* was unsuccessful (Strategy 4) would amount to a higher cost compared to OAM alone.

Average cost effective ratios (ACER) were also determined. ACER estimates the cost per successful eradication of H. pylori infection. Lower ACER signifies a more preferred strategy since a low resource input is consumed for each successful eradication. Using OAM alone had the least ACER followed by OAM plus repeat OCM, OCM alone, and finally OCM plus repeat OCM. However, the strategy with the highest efficacy would be preferred since many patients would be relieved of ulcer. In this analysis, we sought to describe the best alternative to the eradication strategy with the highest efficacy and not necessarily the one with the least cost. Thus Strategy 3 (OCM plus repeat OCM for patients in whom eradication was unsuccessful) was used as the standard for comparison since it has the highest efficacy. Other strategies were compared with Strategy 3. The incremental cost effectiveness ratio (ICER) measured the additional cost incurred for every patient that only the most effective strategy successfully treated. Strategy 4 had the highest ICER followed by Strategy 2 with Strategy 1 having the least ICER. Incremental cost of the strategy with the highest efficacy (Strategy 3) in relation to other strategies was divided by annual cost of relapse treatment. This represents the number of years it would take for the cumulative future cost of treating a patient with relapse treatment, to equal the incremental cost of the most effective eradication therapy and thus, the unit of comparison for evaluating cost effectiveness of the different strategies. As shown in Table 2, it will take 84 years for the cost of future relapse treatment with ranitidine to equal the extra cost of achieving a 1% increase in eradication rate with Strategy 3 (OCM plus repeat OCM) in relation to Strategy 4 (OAM plus repeat OCM). Strategy 2 (OAM) comes next after Strategy 3 with 19 years. The least is Strategy 1 (OCM) with 4 years.

One way and multi-way sensitivity analysis was conducted to test the CEA results to parameters alteration (Table 3). Varying the efficacy of OCM, Strategy 3 had the longest time for future relapse treatment cost to equal its ICER. The same applies when the ICER was estimated with range of efficacy of OAM and re-treatment with OCM. Using minimum or maximum cost of medications in the different strategies did not alter CEA result as Strategy 3 still had the longest time for future relapse treatment cost to equal its ICER.

Table 2: *Differences in outcome between four H. pylori eradication regimen strategy*

Strategy	Cost (Naira)	Efficacy (%)	ACER	*ICER	Time (years) for future relapse treatment costs to equal incremental cost of strategy[Ø]
Strategy 4 - OAM + OCM	₦106,518	94	1,127	80,710	84
Strategy 2 - OAM	₦67,424	85	793	18,518	19
Strategy 1 - OCM	₦260,624	91	2,864	4,115	4
[†]Strategy 3 - OCM + OCM	₦284,080	97	2938	base	Base

OAM = omeprazole, amoxicillin, and metronidazole
OCM = omeprazole, clarithromycin, metronidazole
*ICER represents the additional cost of obtaining 1% increase in eradication rate.
[†]Strategy 3 (OCM plus repeat OCM) has the highest efficacy and was used to determine ICER of other strategies.
[Ø]Incremental cost of strategy 3 in relation to other strategies divided by annual cost (₦966) of relapse treatment.
NB: US$1.00 is equivalent to ₦120.00

Table 3: *Sensitivity analysis to access the cost effectiveness of four strategies for the eradication of H. pylori*

Variable and range	Base estimates	Time (years) for future relapse treatment costs to equal incremental cost of strategy[Ø]		
One-way sensitivity analysis				
Base case estimate		1. OCM	2. OAM	4. OAM + OCM
OCM efficacy (%)	91			
89		3	20	92
92		5	19	61
OAM efficacy (%)	85			
82		4	15	46
87		4	22	92
Re-treatment efficacy (%)	63			
55		5	20	61
71		4	19	184
Multi-way sensitivity analysis				
		1. OCM	2. OAM	4. OAM + OCM
Using minimum cost of the medications		3	16	69
Using maximum cost of the medications		3	18	79

[Ø]*Incremental cost of strategy 3 in relation to other strategies divided by annual cost (₦966) of relapse treatment.*

DISCUSSION

Economic evaluation, often using cost-effectiveness analysis, has become a commonly used tool to inform health policy as well as to guide clinical decisions[12]. The use and application of cost-effectiveness analysis information to guide the priority-setting process of national government and medical decisions in hospitals has remained limited especially in Africa. Trained health economists who can frame the issues properly, and then provide accurate answers, are in chronic short supply[13]. According to one estimate, there are only about 100 health economists in all of Africa; talent is concentrated in just a few countries, and mostly in research and academic centers, rather than in ministries of health, where decisions are taken[14]. This study sought to provide evidence for the use of cost-effective eradication therapies in managing duodenal ulcer disease. Different eradication therapies commonly used in Enugu state were evaluated in order to ascertain which one would result in greater resource saving as well as provide the best value for money.

The result was interpreted using strategy 3, the most efficacious strategy as baseline. In principle, the therapy with the highest efficacy would be the preferred choice in management of ulcer patients. Patient with duodenal ulcer often live a poor quality of life. Thus any intervention that results in rapid ulcer healing and avoids recurrence of ulceration would be the preferred choice. Strategy 3 was the most efficacious and was used as a baseline. Strategy 3 was compared with other strategies so as to access the amount of resources that would be saved by using these other strategies as a replacement. This was done by determining the incremental cost effective ratio. Incremental cost effective ratio (ICER) represents the cost incurred in eradicating *H. pylori* with strategy 3 in an extra patient that the other strategies could not eliminate. Higher ICER indicates a more cost effective strategy. Strategy 4 i.e. omeprazole, amoxicillin, and metronidazole and re-treatment with omeprazole, clarithromycin, and metronidazole had the highest ICER. This simply means that a large amount of money would be spent in using Strategy 3 to eradicate *H. pylori* in an extra patient in which strategy 4 could not eliminate.

To illustrate this graphically, the time for future relapse treatment costs with ranitidine (150mg) twice daily for 4 weeks, was compared with the ICER for each strategy. This showed the time in years it will take for future relapse treatment costs to equal incremental cost of each of the 3 strategies. Again, strategy 4 had the longest time, showing that it is the most cost-effective option compared to the other strategies.

After parameter alteration using one-way sensitivity analysis (Table 3), strategy 3 also had the highest ICER and the longest time for future relapse treatment cost to equal its ICER. Therefore, alteration of efficacy and cost values did not have any effect on the ACER and ICER results. Thus, the major results of this analysis remain robust to the degree of alterations used in the sensitivity analysis.

This study has some limitations. Indirect cost was not included. Indirect cost can make a major difference to the final cost-effectiveness of a particular treatment especially for patients with duodenal ulcer. This is because indirect costs are reduced when patients are ill for a shorter period of time[15]. Resistance to antibacterial therapy which might affect eradication of *H. pylori* and consequently cost of treatment was not considered. However Strategy 3 appeared to be the most cost-effective for the eradication of *H. pylori* in patients with duodenal ulcer. This study recommends the use of omeprazole, amoxicillin and metronidazole in eradication of helicobacter pylori in patients with duodenal ulcer. Patient that still displays dyspeptic symptoms can be re-treated with a more efficacious regimen, omeprazole, clarithromycin and metronidazole.

CONCLUSION

The use of omeprazole, amoxicillin and metronidazole in eradication of *H. pylori* in patients with duodenal ulcer and re-treating with omeprazole, clarithromycin, and metronidazole in patients that still shows dyspeptic symptoms is the most cost-effective option compared to the other 3 strategies. The major conclusions arrived in this analysis still holds even when some of the parameters used in the analysis were subjected to variation. This analysis could guide medical decision making in hospitals or could address the question of public subsidies for the purchase of medicines.

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