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Comparative Cost Effectiveness Analysis of Empirical and Non-empirical Therapy in Pelvic Inflammatory Disease in a Tertiary Health Institution, North-central Nigeria

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Abstract

Background: *Pelvic inflammatory disease (PID) is a leading cause of infertility, ectopic pregnancies and psychological trauma, thus, representing a major public health concern and high economic burden for women in their reproductive ages.As a result, it will be beneficial to identify competing options in drug therapy in order to redirect resources with the aim of achieving more value for money in terms of cost effectiveness.*

Objective: *To conduct a comparative cost-effectiveness analysis of empirical and non-empirical therapy in Pelvic Inflammatory Diseases among patients attending the General out-patient clinic and Gynecology clinic in University of Ilorin Teaching Hospital, North – central Nigeria.*

Methods: *After including a 10% attrition rate, a sample size of 369case notes was derived from a total population of 2, 652 PID patients. A drug utilization study was conducted through a one year retrospective review (January 2021 to December 2021) of the 369 case notes The case notes were selected by systematic random sampling using sampling interval of 5. This was accompanied by using the World Health Organization-defined daily dose method of evaluating drug use. EQ-5D-5L was employed in determining the effectiveness of the identified treatment options in terms of quality adjusted life years (QALYs).*

Results: *One hundred and four of the selected cases (28%) were not tested for PID and were placed on empirical therapy while 265 (72%) were tested and benefited from targeted therapy or non-empirical therapy. The overall Mean Effectiveness obtained expressed as quality adjusted life years (QALY) was 0.578. The overall Mean utility status obtained from the EQ VAS was 74.52. The total cost obtained to access empirical therapy was ₦5,880(14USD) with an effectiveness of 0.637 while the total cost obtained to access non-empirical therapy was ₦8,715 (21USD) with an effectiveness of 0.555.*

In conclusion there was statistically significant difference (P=0.007) in theeffectiveness/outcome of Empirical compared with Non-empirical regimen, with Empirical regimen being more effective and also more cost-effective.

Keywords: Effectiveness, Outcome**,** Cost-Effectiveness Analysis, PID, Empirical, Non-Empirical

Introduction

Pelvic inflammatory disease (PID) is an inflammation of the female upper reproductive/genital tract owing to an infection in women, affecting the endometrium, uterus, fallopian tubes, ovaries,and pelvic peritoneum (Jennings and Krywko, 2021). It is a common disorder of the reproductive tract that is often misdiagnosed and inadequately treated (Das *et. al.,*2016). Estimates by the US Center for Disease Control and Prevention (CDC) showed that more than one million women experience an episode of PID each year taking into account missed or undocumented cases of PID (CDC, 2007). The majority of cases of PID globally, are associated with sexually transmitted infections caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae* (Jennings and Krywko, 2021). In another study (Olowe *et. al.,* 2012) in Oshogbo, Nigeria, about 70% of patients were positive for PID, and the most commonly isolated organism was *Staphylococcus* in 41.4%, followed by *Klebsiella* species in 24.29% of cases.

The diagnosis is made primarily on clinical suspicion, and empirical treatment is recommended in sexually active young women or women at risk for sexually transmitted infections who have unexplained lower abdominal or pelvic pain and cervical motion, uterine, or adnexal tenderness on examination (Curry *et al.,*2019). The global incidence varies from 0.28% to 1.67% (Oroz *et al,* 2012) with a prevalence of 62.8% (Okonm *et al,* 2008). Globally PID is a leading gynecological problem which is associated with socio-economic and psychological costs (Okon *et al,* 2008). It is the cause of about 30% of infertility cases and 50% of ectopic pregnancies, thus presenting a major public health and economic burden, for women in their reproductive age (Al-Kuran *et al,* 2021). This is further complicated by the fact that it is difficult to predict and prevent. Studies by Sartelli *et al* (2017) have hypothesized that the actual burden of PID may be greater than is currently being reported due to the unavailability or unreliability of pathogen screening methods in various countries. A study found out that just 6% of subjects who met diagnosis criteria of the disease were correctly treated with appropriate coverage in an outpatient setting. (Woods *et al.,* 2013). This will definitely lead to more cases of complications (CDC 2015), and this concerning information makes it important to understand the pharmaco-economic burden of treating PID. Studies done by Sweet *et al* in 2011 have described that management of PID and its complications are quite expensive, and similar findings by Spencer (2014), have stated that PID management consumes a major percentage of medical resources from different nations.

The cost of having PID has previously been estimated at $1,995 per patient, not including expenses for future evaluation and treatment of complications (Curry *et al,* 2019). In addition, the estimated annual health care cost for PID and its complications in the United States is over $2 billion (Sweets, 2011). In another study carried out in northern Nigeria by Omole et al, 2011 the total cost of prescribed antimicrobials was reported to be NGN652,38 (US $4,263) with quinolones accounting for the highest amount of NGN261,84 (US $1,711.38). These findings reveal the socioeconomic burden of the management of PID, especially in developing countries like Nigeria, and Africa as a whole. Some local studies agree with this, and have confirmed that the

prevalence of PID in a society negatively correlates with the socio-economic status of the inhabitants, hence PID is more prevalent in resource poor settings such as Nigeria. (Olowe et al 2012, Robert *et al* 2015). It thus becomes more difficult to effectively manage PID in poverty stricken communities, as the cost of management may be too much for the patients to bear for theduration of treatment.

The use of medications in the treatment of patients as regards diagnosis and diseases cannot be overruled. Therefore, there is a need for continuous assessment and cost comparison between regimens used for treatment of diseases particularly PID in Nigeria. This is highly beneficial in resource poor settings and will help bridge the gap between diagnosis and proper treatment, if theaffordable regimens are matched with the right patient. D as *et al* (2016) proposed potential cost- effective approaches that could be employed in real-world settings. This will ensure adherence, and lead to a similar improvement in morbidity and mortality among PID patients. There is evidence that prescribing different outpatient PID treatment regimens based on cost differences, clinical opinion regarding relative efficacy, and medication characteristics lead to greater adherence hence, greater effectiveness compared with regimens without those characteristics (Biegi and Wiesenfeld, 2003). However, these studies were not done in Nigeria, and there is a significant knowledge gap concerning cost effectiveness analysis of PID therapy in Nigeria as studies are few, leading to a paucity of data.

This study was therefore aimed at conducting a comparative cost-effectiveness analysis of empirical and non-empirical therapy in Pelvic Inflammatory Diseases among patients attending University of Ilorin Teaching Hospital, North – central Nigeria. This knowledge would be of benefit in formulating policies that could aid patients living in resource poor settings to access treatment that is rational, cost-effective (value for money), affordable and thus aid adherence, preventing long term morbidity and mortality associated with PID.

Methods

Setting

This study was conducted among patients with pelvic inflammatory diseases at University of Ilorin Teaching Hospital (UITH), Ilorin, Kwara State, Nigeria. UITH has several specialties and1613 bed spaces that cater for patients from Kwara, parts of Oyo, Osun, Ekiti, Kogi states. It is also a known research center with a number of breakthroughs and successful operations such as the Open-heart Surgeries. The General out-patient clinic and Gynecology clinic runs every Monday to Friday.

Ethical Approval

Ethical approval was sought and obtained from the Ethics and Research Committee of the Institution (Approval Number: ERC/PAN/2022/03/0258).

Study Population and Sample Size

The study population comprised of a total of two thousand six hundred and fifty-two)(2, 652 patients with PID registered at the General out-patient clinic and Gynecology clinic of University of Ilorin Teaching Hospital in the last ten (10) years January 2011 to December 2020. Fischer's formula (Araoye, 2013) was applied to determine the sample size from this estimate. The required

sample size was 369.

All cases of recurrent pelvic inflammatory disease who presented for treatment in UITH from ages 18 and above were included in the study while in-patients, patients with co-morbidities and pregnant PID patients were excluded.

Study Design for drug utilization review

A drug utilization study was conducted through a one year retrospective review (January 2021 to December 2021) of the 369 case notes Treatment Options / Drug utilization pattern of the various treatment options available were identified from case-notes of the subjects. The treatment options identified was based on whether diagnostic tests were carried out prior to commencement of therapy. This served as the basis for the identification of empirical and non- empirical regimens.

Study design for cost- effectiveness analysis

A prospective study was conducted among patients with recurrent PID at the General out-patient clinic and Gynecology clinic of University of Ilorin Teaching Hospital, Ilorin, Kwara State. This was done to determine effectiveness of their therapy. Data relevant to the study were collected using a European Quality of life five-dimensional five-level (EQ5D5L) standardized questionnaire. This is a renowned generic instrument measuring quality of life in different diseases; it includes 5 dimensions (mobility, self-care, daily activities, pain-discomfort, anxiety and depression) and a Visual Analogue Scale (VAS) that evaluates patients' perceived utility status (Balestroni *et al,* 2007).

After all available treatment options were identified (empirical therapy and non-empirical therapy). A utility value was determined for patients on the two identified regimens the overall utility value for all patients on both regimen and overall EQVAS score / Visual analog scale (VAS) were also determined. The QALY is obtained by multiplying the duration of time spent in a health state by the HRQoL weight (i.e. utility score) associated with that health state. This was done by multiplying the overall utility and the duration of therapy for the administration of the drugs used in the management of PID.

Data Collection Procedure

The selected patients from the retrospective review (chosen from January 2021 to December 2021) were coded with the assigned hospital numbers on each of the selected369 case notes, and the appointment days of each patient noted. Our team were present on all appointment days, identified the patients with case note numbers/code and administered the questionnaires at the point of exit of each patient from the consultation rooms .The signature of each researcher was appended to the case notes to prevent multiple administrations of the questionnaire to the patients.

Cost Measure

The following direct costs were considered in measuring cost for each patient:

- Costs of medications (from the pharmacy price list)
- Cost of diagnostic tests (from the laboratory/radiology)
- Cost of Physician consultation (from Health Information department of the Hospital)

- Estimated cost of transportation (from National Union of Road Transport WorkersNURTW)

- Cost of personnel (from accounts department of the hospital)

For cost of medications, costs were obtained from the Pharmacy Department and the cost per defined daily dosage (DDD) of antimicrobial used for each patient was calculated. DDD units are recommended standard by WHO for drug use analysis. One DDD usually represents the daily dosage of antimicrobial per day.

Cost Effectiveness Analysis (CEA)

Cost Effectiveness Analysis enables a decision-maker to make an informed decision about a preferred choice among possible alternatives. It indicates the intervention that provides highest value for money. It involves calculating and comparing the cost (resources needed for intervention implementation) and the effectiveness (outcome). The incremental cost-effectiveness ratio (ICER), was computed using the formula given below, the ICER value obtained was used to determine comparative effectiveness of the treatment options.

$$\frac{\text{change in cost}}{\text{change in effectivenes}} = \frac{\text{cost of option A} - \text{cost of option B}}{\text{effectiveness of A} - \text{effectiveness of option B}}$$

Data Analysis

The data obtained were analyzed using descriptive and inferential statistics. The data collected were entered into and analyzed using Statistical Package for Social Sciences (SPSS) version 25, computer software packages. In carrying out the different analyses, 95 % CI and p-value of 0.05 were used for deciding statistical significance of differences observed.

Exchange rate

During the period of this study, 1USD equaled 415 Naira

Results

Out of the 369 patients reviewed, 104 (28%) had no diagnostic test done for PID and were placed on empirical therapy while 265 (72%) were tested and benefited from targeted therapy.

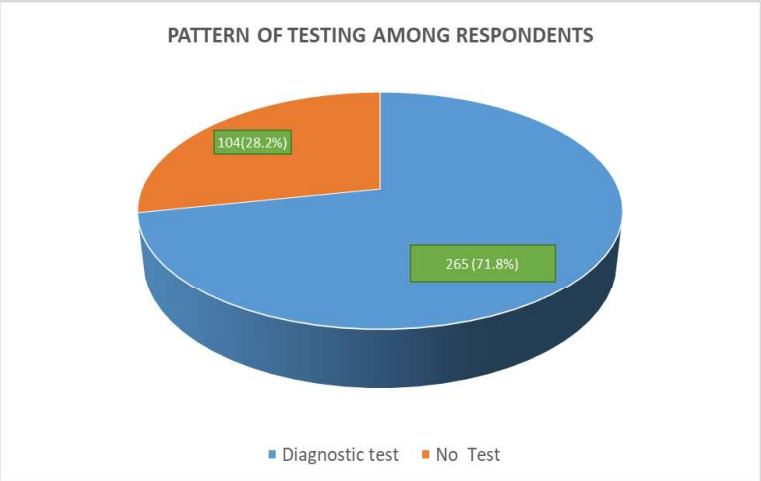

Figure 1: Distribution of respondents based on diagnostic tests

Effectiveness Analysis

The overall mean effectiveness obtained expressed as quality adjusted life years (QALY) was 0.578.The overall mean utility status obtained from the EQ VAS was 74.52. Table 1 shows the p- value obtained as 0.007

TABLE 1: Relationship between regimen and outcome

Regimen	Non Empirical	Empirical	Total	X^2	*p*-value
QALY score	N = 265(71.8%)	N = 104(28.2%)	N = 369(100%)	1.615	0.007
<0.5	158(59.6)	56(53.8)	214 (57.9)		
>0.5	107 (40.4)	48(46.2)	155(42.1)		

Cost-Effectiveness Analysis

The total cost accrued to access empirical therapy was ₦5,880 with an effectiveness of 0.637 while the total cost accrued to access non-empirical therapy was ₦8, 715 with an effectiveness of 0.55 .

Table 2: Cost-effectiveness analysis (cea) for empirical and non- empirical regimen

TREATMENT OPTION	TOTAL COST(C) Naira (USD)	EFFECTIVENESS(E)	(C/E)	ICER ($/QALY)
NON-EMPIRICAL (Option A)	8715 (21)	0.555	₦15, 702/ unit of E	- 85, Dominated
EMPIRICAL (Option B)	5880 (14)	0.637	₦9, 230/ unitof E	

*QALY - Quality Adjusted Life Years.
*ICER-Incremental Cost Effectiveness
* During the period of this study, 1USD equaled 415 Naira

Discussion Effectiveness Analysis

This study revealed that majority of respondents were placed on non- empirical regimen for PID, while few were on empirical regimen the overall mean utility status of patients with PID from the EQVAS score / Visual analog scale (VAS) was 74.52, this showed their therapy was effective. This is similar to findings by Smith et al who found an ambulatory mean EQVAS score of 70 in PID patients. (Smith et al, 2008) This is probably due to the fact that patients in both studies had undergone some form of antibiotic therapy at the time of these studies and which had a positive effect on the health status. It has been reported that PID patients who have complications have been found to have lower health status scores (Smith et al, 2008).This study had an overall mean QALY score of 0.578 for patients diagnosed with PID. This is much higher than the mean QALY score of 0.1 obtained by Looker et al among untreated females with PID in Scotland (Looker *et al*, 2015).

While comparing the regimens in the index study, there was found to be a higher proportion of patients on Empirical antibiotic regimen with a higher QALY score, than among those on Non Empirical therapy (46.2% to 40.4%). This is statistically significant, and may suggest that QALY may be a more accurate means of determining effectiveness of therapy, as previous studies based on clinical cure have failed to find any conclusive evidence that one regimen was superior to another (Savaris, 2018). Haggerty et al compared several approved mono and combination regimens for the treatment of PID and found similar clinical cure rates ranging from 90% -97%. (Haggerty *et al,* 2010). Patient and provider adherence may be a factor in improving Empirical therapy outcomes in PID management especially in the underdeveloped countries, as delay in commencement of therapy due to diagnostic procedures, as well as the added financial burden of testing may tend to discourage patients from complying with the regimen.

There was statistically significant difference in the effectiveness/outcome of empirical compared with non-empirical regimen, with empirical regimen being more effective

(utility score of 0.637). The cost for an empirical treatment of PID in UITH was found to be ₦5880 (14USD). This shows that an empirical therapy regimen is cheaper with high effectiveness outcome, therefore more cost effective. The cost for a non-empirical treatment of PID was found to be ₦8715 (21USD) with a utility value of 0.555 for its effectiveness, showing that this regimen is more expensive than the former but not more effective. More so, an ICER value of -85 was obtained, showing that the empirical treatment dominated the non-empirical, making the empirical more cost-effective. This is because while patients on empirical therapy procure drugs alone, patients on non-empirical therapy may first need to carry out more than one diagnostic tests which confirms diagnosis as well as microbial sensitivity to drugs thereby, incurring more out-of-pocket costs. Savaris et al report no clear difference between outcome rates on different regimens currently used or in trial (Savaris, 2017). Thus while Non Empirical therapy may help isolate offending microbial agents, it offers no added benefit, especially in low-income resource country where added diagnostic and screening costs affect adherence to medication and ultimately worsen outcome of PID, causing sequel that end up reducing the overall effectiveness of Non empirical regimens. Efforts should however be made to improve PID prevention strategies. (Scholes *et al*, 1996).

Majority of the respondents (265; 72%) were on non- empirical regimen while 104 (28%) were on empirical regimen. The overall mean effectiveness obtained expressed as quality adjusted life years (QALY) was 0.578. The overall mean utility status obtained from the EQ VAS was 74.52.There was statistical significant difference (p=0.007) in the effectiveness/outcome of Empirical compared with Non-empirical regimen, with Empirical regimen being more effective, and also more cost effective.

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