Comparing the Cost-Effectiveness of the ^{14}Carbon-Urea Breath Test and Histology for the Detection of *Helicobacter pylori*

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Abstract

Approximately 4000 patients are diagnosed annually with *Helicobacter pylori (H pylori)* infection at King Edward VIII Hospital, KwaZulu-Natal, South Africa. The current method employed for the detection of *H pylori* is the histological analysis of a biopsy specimen taken at endoscopy.

Recently, in South Africa, health budgets devolved from central to provincial governments making each institution responsible for its own budget. This required some changes in strategy in order to find a more cost-effective means of diagnosis without compromising service delivery.

This study was undertaken to evaluate and compare the Carbon-14 Urea Breath Test (^{14}C-UBT) with histology for the detection of *H pylori* in terms of cost-effectiveness.

Fifty-two patients, aged between 18-80 years, clinically diagnosed with gastritis and referred for endoscopy were studied. Each patient was assessed by endoscopy with biopsy for histology and a ^{14}C-UBT.

The sensitivity and specificity of the ^{14}C-UBT were determined so as to ensure reliability of the ^{14}C-UBT when compared to histology for the detection of *H pylori*. The sensitivity of the ^{14}C-UBT was calculated to be 82% and the specificity 70%.

The provincial public sector cost of the ^{14}C-UBT was calculated to be R135,42 and of the histology inclusive of a biopsy taken on endoscopy was R308,33.

The findings of this study clearly indicate that the ^{14}C-UBT provide a more cost-effective option as compared to histology for the detection of *H pylori* infection.

Background

The current method employed for the detection of *H pylori* is the histological analysis of a biopsy specimen taken on endoscopy. Although Leung and Sung consider histology the 'gold standard' for the detection of *H pylori* it is not without drawbacks [1].

It involves an invasive, expensive endoscopy that is not always easily tolerated by patients. Some 4000 patients are diagnosed annually with *H pylori* infection at King Edward VIII Hospital (KEH), a major hospital and training institute based in KwaZulu-Natal, South Africa.

The recent devolution of health budgets from central to provincial governments in South Africa and the fact that each institution is responsible for its own budget requires some changes in strategy [2]. KEH is one such institution, with major budget constraints.

H pylori, is a helical shaped gram-negative bacterium found in the human stomach. It is the major cause of peptic ulcer disease and is recognized as a group 1 carcinogen for gastric carcinomas [3,4].

Many varied techniques have been described for the diagnosis of *H pylori* infection. The methods are either invasive and direct or non-invasive and indirect. They vary in cost, simplicity and patient acceptability [5]. However, the actual costs of the tests have not been quantified in the literature reviewed. It is therefore necessary to employ a non-invasive, cost-effective and acceptable procedure to detect *H pylori* infection in an attempt to seek alternate approaches without compromising service delivery. The ^{14}C-UBT is used internationally for *H pylori* diagnosis.

Sensitivities of between 90-97% and specificities of between 89-100% have been reported for the ^{14}C-UBT [6].

What is *Helicobacter pylori*?

The *H pylori* bacterium adapts to the acidic environment of the stomach by acting upon endogenous urea using its enzyme, urease [4,5]. Urease converts the urea that is normally found in the stomach to bicarbonate and ammonia. *H pylori* bacteria become embedded in the mucus lining of the stomach and this makes it impossible for the body's immune system to eradicate them [4,7]. The white cells dispatched by the immune system to the gastric mucosa are unable to penetrate the gastric mucosa easily. These polymorphs then die often causing a further immune response. This results in an inflammation of the gastric mucosa leading to a gastric or peptic ulcer [7]. *H pylori* has been implicated in the pathogenesis of gastritis, gastric and duodenal ulcers and gastric carcinomas [8]. Peptic ulcers are caused by acid damage in areas of the mucosa that are weakened by inflammation due to *H pylori* infection or other agents, for example, non-steroidal anti-inflammatory drugs [3].

In gastric cancer, both types of neoplasms, that is, intestinal and diffuse tumors have been linked to *H pylori* infection [3]. Greenberg, Koch and Cello [9] report that the recurrence of peptic ulcers in-patients who have been treated for *H pylori* infection is significantly decreased.

In the clinical setting *H pylori* infection is related to ulcer recurrence as 55 to 90% of ulcers recur when treated with only proton-pump inhibitor or H2 therapy as opposed to less than 5% recurrence when triple therapy for *H pylori* infection is added [10]. These statistics are important when considering the follow-up assessments of patients in the detection of *H pylori* infection post-eradication. Desroches *et al* [10] from the University of Montreal, Canada report that the Consensus Development Conference of National Institutes of Health recommend that patients with peptic ulcer disease with *H pylori* infection receive antimicrobial therapy.

Epidemiology of *H pylori* Infection

H pylori infects about 30% of the population of Western Europe and the United States of America (USA) and about 80% of the population of developing countries [11]. The presence of *H pylori* infection varies with race, nationality, socioeconomic status and water source. The high prevalence of *H pylori* infection could be related to the source of water especially in developing countries. In the USA, Blacks and Hispanics have a higher prevalence of *H pylori* infection than Whites [12]. A study done in 1994 by Sathar *et al* [13] in KwaZulu-Natal, South Africa showed that there was a higher prevalence of *H pylori* infection in the African (93%), Indian (83%) and Coloured (81%) populations than the White (42%) population. Malaty *et al* [14] reported that the prevalence of *H pylori* infection is twice as great among Blacks as in Whites. In another study undertaken in South Africa by Louw *et al* [15] it was shown that the prevalence of *H pylori* infection was 40% in Whites and 71% in Coloureds.

Testing for *H pylori*

The tests available for the diagnosis of *H pylori* differ with respect to invasiveness, cost, sensitivity, specificity and in the additional information that they can provide [5]. The ideal test for the detection of *H pylori* infection should have a high sensitivity and specificity. It should be relatively easy to perform and inexpensive, using routine equipment and techniques. Ideally the test should be non-invasive or minimally invasive. The patient should be able to tolerate the test well [6].

Methods of detection of *H pylori* have been categorized as direct and invasive or indirect and non-invasive. Invasive methods include histology, culture, and rapid urease tests. Non-invasive methods are serology and urea breath tests (UBTs) [16].

Invasive methods include the tests performed on biopsy specimens taken on endoscopy. Invasive tests explore only a small part of the surface of the stomach mucosa and it is therefore possible that when taking a single-biopsy-specimen, the result may be falsely-negative [16].

Serology, is a non-invasive, indirect method which is relatively easy to perform and is the cheapest of all the methods described for the detection of *H pylori* [6,17]. Brown and Peura [6] in their work describe the benefits of serology, namely, that it is easily accepted by patients, it has sensitivities of 88 to 99% and specificities of 86 to 95% that compare well to histology and culture and its low cost. However, Boyce [18], Brown and Peura [6], Fauchere [17] and Peura *et al* [19] in their respective studies mention an important drawback of serology, in that it is an unreliable method for evaluating patients after bacterial eradication therapy as the antibody may persist for up to one year, so that serology may remain positive in most patients. It is important to re-assess patients following eradication therapy to ensure complete absence of disease since if it is left untreated *H pylori* infection, may lead to peptic ulcer disease and gastric carcinoma [3].

Another method of detection of *H pylori* infection is the labelled carbon urea breath test which relies on the efficiency of *H pylori* to hydolyse urea. Carbon-13 urea breath tests (^{13}C-UBT) and Carbon-14 urea breath tests (^{14}C-UBT) utilise the principle that in the presence of *H pylori* urease, the urease is hydrolysed and the released isotopically labelled carbon dioxide is exhaled in the expired breath [20]. The labelled carbon is administered orally and, in patients with an *H pylori* infection, the urea is metabolised to ammonia and carbon dioxide. This labelled carbon dioxide may be quantified [6].

Unlike the biopsy-based methods of detection of *H pylori* infection, in a Urea breath test (UBT) the isotope coats the entire gastric mucosa and it is hence not susceptible to sampling error [20]. UBTs are highly accurate yet simple, non-invasive, relatively inexpensive tests for the detection of *H pylori* infection [21, 22]. Both Logan and Faigel *et al* in their respective work [21, 22] mention that UBTs are relatively inexpensive, the actual cost of a UBT was not quantified.

The UBT, unlike serology may be used as soon as one month after the completion of *H pylori* eradication therapy to assess patients [21, 23]. Since UBTs do not involve the taking of blood or working with the body fluids of patients, they are considered relatively safe for medical personnel as the exposure to diseases such as hepatitis and HIV/AIDS (Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome) is non-existent. Unlike biopsy-based methods, UBTs are rapid, safe and free from observer bias [22].

It is evident from the literature reviewed that there is a gap in the research on the reporting of the actual costs of methods of detection of *H pylori*. Megraud [16] in his work explains that it is difficult to give the exact costs of the tests as few studies have focused on this aspect.

Study Method

Fifty-two consenting patients aged between 18-80 years, who had a clinical diagnosis of gastritis and were referred for endoscopy, were studied. Due to the use of radioactivity, pregnant and lactating females were excluded. Patients on any antibiotics or bismuth preparations for 4 weeks prior to the study were excluded as these preparations could produce false-negative results.

Each patient had an endoscopy with an antral biopsy performed by an endoscopist at which the researcher was present. A histological analysis was then performed on the biopsy specimen. This was followed by a ^{14}C-UBT done by the researcher using the method as described by Marshall *et al* [24].

The costs of the ^{14}C-UBT and of histology per patient were determined employing a cost-effective analysis by identifying the different cost elements, that is, fixed and variable costs associated both tests. Each cost element, namely, equipment, materials, personnel salaries, rental (land and buildings) and utilities (water, electricity and telephone) was considered individually and apportioned per test. In order to determine the cost of histology, the cost of an endoscopy and a biopsy were included. Provincial costs were considered in all cost calculations.

^{14}C-Urea Breath Test

- Equipment

  i) Liquid scintillation counter (LSC)

  Following discussion with the vendors, the lifespan of a liquid scintillation counter was taken to be 15 years. The capital cost, that is, the replacement cost of an LSC was divided by the lifespan. To this was added the annual service contract fee. Seventy (70) vials per day could be counted during an eight-hour working day.

  (ii) Refrigerator

  The cost of a refrigerator required for the storage of Carbon-14-Urea, was obtained and a lifespan of 15 years was considered. The total costs of the equipment were apportioned per patient.

- Materials

  Prices of the breath collection apparatus, collection vials, Carbon-14, liquid scintillation fluid, hydroxide of hyamine, ethanol, phenolphthalein and calcium granules, were obtained from the suppliers. This cost was apportioned per patient depending on the quantity of each item used per patient. Prices of disposable gloves, syringes and needles were also included in the costing. The cost per patient was worked out for the materials.

- Salaries

  The midpoint of the personnel salary scales were obtained from the personnel department at KEH for each category of staff required for the test. The salaries of a nuclear medicine radiographer, radiologist, clerk and messenger/cleaner were considered. The time spent per patient was established and it was taken that 15 patients per day could be examined. The salaries were divided accordingly.

- Rental

  After discussions with real estate agents and a provincial health economist, a rental for the required floor space was established. This figure was divided to determine cost per patient.

- Utilities

  Permission from the medical superintendent of KEH to peruse the hospital's utilities bills was not received. The health economist suggested market related estimates for the departmental electricity, water and telephone expenses be used. These costs were apportioned per patient.

Histological Analysis

- Equipment

  (i) Endoscope

  After discussion with the chief clinical technologist at the GI Unit at KEH and, the vendors, it was estimated that the lifespan of an endoscope was equivalent to being used in approximately 2000 examinations. The cost of an endoscope was divided by

Table 1: *Calculation of Costs of the ^{14}C-UBT and Histology*

RESOURCE	^{14}C-UBT	COST PER PATIENT IN RANDS	HISTOLOGY	COST PER PATIENT IN RANDS
EQUIPMENT	Liquid Scintillation Counter	1.28	Endoscope	69.50
	Breath Collection Equipment	0.03	Viewing Monitor	1.44
	Refrigerator	0.04	Clip-on Camera	14.10
			Processor	13.50
			Light Source	4.57
			Suction Pump	0.39
			Biopsy Forceps	27.00
			Microscope, Slide	1.30
			Microtome Cutting Block	0.70
MATERIALS	^{14}Carbon-Urea	33.50	Detergent	9.30
	Liquid Scintillation Fluid	2.64	Brushes	18.00
	Hydroxide of Hyamine	12.16	Anaesthetic Spray	0.85
			Antispasmodic	13.00
	Calcium Chloride Granules	2.00	Stain	0.41
	Phenolphthalein Indicator, Ethanol			
	Gloves, Gowns/Aprons	2.00	Gloves, Gowns/Aprons	2.05
	Liquid Scintillation Vials	4.02		
PERSONNEL	Radiographer	22.91	Medical Technologist	4.90
			Pathologist	16.18
	Nuclear Medicine Physician	32.35	Endoscopist	32.35
	Clerk, Messenger/Cleaner	22.13	Staff Nurses	23.56
			Clerks, Messengers/Cleaners	44.26
UTILITIES	Water, Electricity, Telephone	2.67	Water, Electricity, Telephone	4.47
BUILDINGS	Rental	5.00	Rental	5.00

2000 to obtain the cost per patient for use of an endoscope.

(ii) Viewing monitor, clip-on-camera, processor, light source and suction pump

The costs were obtained for each of these pieces of equipments. Each item was estimated to have a 4-year-lifespan.

(iii) Biopsy Forceps

The cost of a biopsy forceps was obtained. The lifespan of a biopsy forceps is approximately 100 patients. The cost of all the equipment was determined and calculated for fifteen patients per day.

(iv) Microscope and microtome cutting block

The cost of a microscope and microtome cutting block were obtained from the vendors. The lifespan was given at 5 years for each of these. The cost of an annual service contract was considered. Costs were apportioned at 50 patients per day. The cost for the use of equipment was calculated per patient.

- Materials

The cost of cleaning brushes, detergent, anaesthetic spray, antispasmodics, syringes, needles, patient gowns and collection material for biopsy material were obtained and apportioned accordingly. After discussion with the chief medical technologist at the histology laboratory at KEH, prices for a haematoxylin and eosin (H&E) stain were obtained. The cost of aluminium ammonium sulphate, chloral hydrate, citric acid, sodium acetate, haematoxylin, dpx mount, eosin, specimen slides and gloves were apportioned per patient by considering the amount of each item used per patient.

- Salaries

Midpoint salary scales of an endoscopist at 15 patients per day, medical technologist at 10 patients per hour, a pathologist at interpreting 30 specimens per day, two staff nurses, two clerks and two messengers/cleaners, were apportioned accordingly per patient.

- Rental

The rental was determined similarly to that for the ^{14}C-UBT except that a larger floor space was required for the endoscopy suite and the histology laboratory. The cost of rental was apportioned per patient.

- Utilities

The calculation of the utilities bills were determined similarly to the bills for the ^{14}C-UBT. The cost of utilities were calculated per patient.

Sensitivity and Specificity

The sensitivity of the ^{14}C-UBT was obtained using the internationally recognized formula for

$$sensitivity = \frac{a}{(a+c)}$$

where *a*, is the number of true positive test results and *c* is the number of false negative test results [25].

The formula

$$specificity = \frac{d}{(b+d)}$$

where *b* represents the number of false positive results and *d* the number of true negative results was used to obtain specificity of the ^{14}C-UBT [25].

Results: Tables 1 and 2

The public sector cost of a ^{14}C-UBT was calculated to be **R135,42** and that of histology to be **R308,33**.

The sensitivity of the ^{14}C - Urea Breath Test was calculated to be 82%. The 95% Confidence Interval for the sensitivity of this test is between 65 - 92%.

A specificity of 70% was obtained for the ^{14}C - Urea Breath Test. The 95% Confidence Interval for of the specificity is between 47-86%.

Table 2: *Summary of the Cost Elements*

	^{14}C-UBT	HISTOLOGY
EQUIPMENT	1.35	132.50
MATERIALS	56.32	43.61
PERSONNEL	77.39	121.25
UTILITIES	2.67	4.47
BUILDINGS	5.00	5.00
TOTAL COST	**135.42**	**308.33**

Discussion

A cost-effective analysis (CEA) compares different options to find the least costly method of achieving a similar outcome [26]. The options considered in this study were the cost of a ^{14}C-UBT and the cost of a histological analysis for the detection of *H pylori*. It has been clearly established from the sensitivity and specificity values obtained for this study, that the ^{14}C-UBT performs as well as histology in achieving the objective of making the diagnosis of *H pylori* infection. It is then appropriate to compare the costs of both the ^{14}C-UBT and histology using a CEA.

The ^{14}C-UBT has been shown to be a cost-effective test for the detection of *H pylori*. Since the ^{14}C-UBT is an inexpensive, non-invasive procedure to detect *H pylori* infection, it may be employed in a public-sector hospital where there is a strong emphasis on cost containment without compromising patient care.

Patients who are treated for *H pylori* infection could in future have a ^{14}C-UBT to check for eradication of the bacterium. Currently due to cost constraints at KEH, no post-eradication test is done. Should the ^{14}C-UBT be implemented, this would benefit the patient and the institution as untreated or incompletely eradicated *H pylori* infection could imply the progression of disease to ulcers and carcinomas. The institution should in the long term benefit financially from treating and checking patients post-eradication of *H pylori* infection, rather than treating possible resultant ulcers and carcinomas.

The ^{14}C-UBT could thus be used as a cost-effective diagnostic tool for the initial diagnosis and post eradication assessment for the detection of *H pylori* infection.

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