EMPIRIC TREATMENT BASED ON *HELICOBACTER PYLORI* SEROLOGY CANNOT SUBSTITUTE FOR EARLY ENDOSCOPY IN THE MANAGEMENT OF DYSPEPTIC RURAL BLACK AFRICANS

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Background. Evidence that chronic gastric *Helicobacter pylori* (HP) infection is an aetiological factor in dyspepsia, peptic ulcer disease, gastric carcinoma and lymphoma has led to the suggestion that all serologically positive dyspeptic patients should be treated empirically with antibiotics to eradicate the infection, without endoscopic diagnosis. The following study was performed to determine whether such a policy would prove to be of benefit in rural Africa, where endoscopic facilities are lacking and infection rates high.

Methods. Four district clinics were visited and 97 consecutive patients with persistent upper gastro-intestinal symptoms studied. After history-taking and physical examination, a blood sample was taken for HP serology (IgG anti-HP EIA) and endoscopy was performed.

Results. In comparison with similar studies in westernised countries HP was considerably more common (80%), and similar to that reported for the background population (83 - 86%), but peptic ulceration (17%) and gastric cancer (1%) were not. HP status and antibody levels failed to predict the presence of serious disease; patients with 'alarm' signs (78%), cancer (78%) and peptic ulcers (81%) had similar seropositivity rates to patients with non-ulcer dyspepsia (81%). Interestingly, many patients with distal oesophagitis were seronegative (40%). Haemoglobin concentrations and nutritional status were similar in HP-positive and negative patients. On the basis of published decision analysis strategies, empiric treatment of HP-positive patients with

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uncomplicated dyspepsia could be expected to produce symptomatic relief in 50% of cases, but would have delayed the diagnosis of 3 cases of cancer if patients over the age of 45 were included.

Conclusion. The lack of association between HP serology and upper gastro-intestinal disease indicates that serological investigation cannot substitute for endoscopy in the management of black Africans with dyspepsia, and that empiric anti-HP therapy cannot be justified.

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The role of HP infection in the recurrence of peptic ulcer disease has revolutionised management of the condition.[1] Although the infection is resistant, triple therapy with antibiotics is effective in eradicating over 80% of infections and thereby reducing ulcer recurrence from 50 - 80% to less than 5%.[2,3] The infection has also been linked to gastric cancer[4] and gastric MALT lymphoma,[5] the strength of the association leading the World Health Organisation to proclaim HP an environmental carcinogen.[6] These developments have led many authorities to recommend antibiotic treatment for all detected HP infections,[7] and others to go one step further and advise eradication of the infection from the environment.[8] The detection of circulating antibodies to HP in the bloodstream has reduced the need for endoscopy and opened the possibility for population screening. With regard to the management of dyspepsia in the community, a number of publications, based on decision analyses, have concluded that empiric treatment of HP-positive individuals will be more cost-effective than initial endoscopy and specific therapy.[9,10]

There remains, however, concern that this practice will lead to the overuse of antibiotics, the emergence of antibiotic resistance in the community, and the eradication of infections that have yet to be proved harmful. While the causative role of the infection in type B gastritis[11] and in peptic ulcer recurrence[2,3] is well established, the strength of the evidence linking the infection to the causation of peptic ulcer disease *per se* and neoplastic disease is weaker, as most infected people do not develop ulcers or cancer. Furthermore, communities with the highest prevalence rates of the infection, for example black Africans, do not appear to have particularly high rates of peptic ulcer disease or gastric neoplasia.[12] A further argument against widespread eradication is the emerging evidence that HP infection may even reduce the risk of other gastro-intestinal diseases.[13,14]

With these questions in mind, we conducted a study to compare HP serology to endoscopic findings in rural black African dyspeptics in order to determine whether empiric anti-HP therapy could substitute for endoscopy. This information is critical for the future planning of health facilities in rural Africa, where endoscopy is unavailable.

METHODS

Study design

A mobile endoscopy team, consisting of two physician endoscopists and two trained endoscopy nurses, visited a number of district and rural hospitals in the Ciskei and Transkei regions of the Eastern Cape province of South Africa. The hospitals and neighbouring clinics were advised of the visit beforehand so that they could encourage patients with undiagnosed gastro-intestinal problems to attend outpatients at the time of the visit. After evaluation of the history and clinical assessment, patients with chronic upper gastro-intestinal symptoms and dyspepsia (defined as 'intermittent or continuous pain or discomfort in the upper abdomen, with or without heartburn, that has been present for a month or more'[15]) were selected for study. Investigations included measurement of the haemoglobin concentration and HP antibody levels, and upper gastro-intestinal endoscopy with biopsy and brush cytology. Informed consent was requested from patients on selection, the protocol having been passed by the University of Cape Town Medical Ethics Committee.

Survey population

A total of 97 black (Xhosa) patients fulfilled the criteria for inclusion in the study. Thirty-five were from Cecelia Makiwane Hospital in Mdantsane (semi-urban) in Ciskei, 22 from Peddie Hospital in Nompumalelo in Ciskei (rural), 29 from S S Gida Hospital in Keiskamahoek in Ciskei (rural), and 11 from Holy Cross Hospital, near Flagstaff in Transkei (rural). Forty-six were male and 51 female, the median age being 51.5 years (range 14 - 90 years).

HP serology

Serum derived from 10 ml venous blood samples was frozen at –20°C for transportation back to the laboratory. HP IgG antibody levels were measured using a commercial test kit (CobasCore Anti-H. Pylori EIA; Art. 07 3497 7: Roche, UK), a second generation two-step enzyme immunoassay. For qualitative assessment, a cut-off level of 100% separated positive from negative, giving a quoted sensitivity of > 95.5% and specificity of > 97.7%. Photometric optical density recordings were used as an index (% units) for quantitative measurements, the intra-assay coefficient of variation being < 5.0% and the inter-assay coefficient of variation < 7.0%

Endoscopy

Endoscopy was performed in theatre under light intravenous sedation (midazolam 2.0 - 3.5 mg) and using a xylocaine

pharyngeal spray. The presence of macroscopic disease in the oesophagus, stomach and duodenum was documented. Single mucosal biopsies were taken from the distal oesophagus, gastric fundus and antrum in all patients, plus additional biopsies from sites of disease if clinically indicated. Samples were preserved in formalised saline for transportation to the laboratory for analysis. In addition, brushings were taken from the mid- to lower third of the oesophagus, smeared onto slides, and fixed with ether/alcohol/PEG spray.

Histological preparation

Biopsy specimens were coded by clinical staff so that they could be examined by one experienced histopathologist (JN) under blinded conditions. After overnight processing, 4 μm paraffin block sections were cut at two different levels.

All sections were routinely stained with haematoxylin and eosin. In addition, Giemsa stains were performed on all gastric biopsies for identification of HP bacteria by 40 x high-power oil-immersion microscopy.

Statistics

Differences between the subgroups of patients were evaluated using the unpaired Student's *t*-test if normally distributed, or Mann-Whitney non-parametric testing if not. The chi-square test was used to compare subgroup seropositivity rates. Results are quoted as group mean ± standard error (SE). The level of significance was taken as $P < 0.05$.

RESULTS

Serology

The mean antibody level of all dyspeptics was 572 ± 75 units, with 80% having levels over 100 and therefore being defined as HP-positive. Equal proportions of males and females were positive, and patients over 40 years of age had a similar infection rate (78%) to those under 40 years (81%). Body mass indices were similar (HP-positive 26.0 ± 1.0 and HP-negative 27.0 ± 2.7 kg/m^2), as were haemoglobin concentrations (13.4 ± 0.3 and 12.3 ± 0.6 g/dl, respectively). Patients with uncomplicated dyspepsia had a slightly (but not significantly) lower rate of positivity (74%) than patients with 'alarm' symptoms and signs (i.e. dyspepsia plus weight loss > 5 kg, dysphagia, early satiety and vomiting, haematemesis and/or melaena, abdominal mass/enlarged lymph nodes) who had a mean positivity rate of 80%.

Endoscopic findings

No abnormality could be seen during endoscopy in 40 patients (41%). Biopsy showed that 60% of these patients had microscopic evidence of gastritis, and in half visible HP organisms could be identified on the mucosa by Giemsa staining. Macroscopic gastritis was seen in 19 (20%) and confirmed histologically in 16. HP organisms were seen in association with gastritis in only half of the sections, although 87% of these cases were serologically positive. The overall breakdown of the 97 dyspeptic patients into diagnostic subgroups based on the combination of endoscopic (macroscopic) and histological (microscopic) findings is summarised in Table I. Nine patients had duodenal ulcers, and 7 gastric ulcers. HP organisms were identified by microscopy in 5/9 and 4/7. One of the gastric ulcer patients was a regular user of non-steroidal anti-inflammatory drugs (NSAIDs).

Table I. Summary of the diagnostic findings based on endoscopic, histological and cytological examination in 97 consecutive black African dyspeptic patients (group mean ± standard error)

Final diagnosis	*N*	Age (yrs)	BMI (kg/m^2)
Non-ulcer dyspepsia	66 (67%)	51 ± 2	26.6 ± 1.2
Normal	21		
Gastritis	24		
HP gastritis	21		
Peptic ulcer	16 (17%)	50.4 ± 4	27.2 ± 2.3
Duodenal ulcer	9		
Gastric ulcer	7		
Cancer	10 (11%)	65 ± 6	19.3 ± 2.6
Oesophageal (squamous cell)	8		
Gastric	1		
Duodenal	1		
GORD	5 (5%)	47 ± 5	21.0 ± 3.8
Total	97 (100%)	52 ± 1.7	25.5 ± 1.0

BMI = body mass index; GORD = gastro-oesophageal reflux disease.

The 6 patients suspected of having oesophageal cancer on clinical grounds (i.e. severe weight loss plus dysphagia), plus an additional 3 without dysphagia, were found to have lesions in the middle or lower third of the oesophagus. The diagnosis of cancer was confirmed in 8; by cytological examination in 7 and by both cytological and histological examination in 5. Of the 2 who were cytologically negative, 1 had histological and cytological evidence of an acute bacterial infection and the other histological evidence of acute-on-chronic oesophagitis; the cytology slide was uninterpretable owing to poor fixation. One early lesion, in the form of a nodule at 28 cm, was detected in a patient with simple dyspeptic symptoms. Cytological examination showed malignant cells, and histological examination severe dysplasia with possible early invasion. Atypical cells were seen on the cytology slides in a further 9 asymptomatic patients, and a low-grade squamous intra-epithelial lesion in 1 patient. Human papillomavirus was identified histologically in 2 severely malnourished dyspeptic patients with active pulmonary tuberculosis. Endoscopic

abnormalities suggestive of reflux oesophagitis were seen and confirmed histologically in only 5 patients.

Antral deformity due to carcinomatous infiltration was proved histologically in 1 patient. In 1 severely malnourished patient, an unusual tumour (an adenocarcinoma) was found in the second part of the duodenum, possibly invading from the pancreas. One patient with no obvious disease on endoscopy was found to have moderate dysplasia on antral biopsy, and histological gastritis in the fundus.

Correlation between endoscopy and serology

Fig. 1 shows that overall 80% of patients were HP-positive and that there were no significant differences in the HP seropositivity rates between the subgroups defined by endoscopic investigation. However, the highest rate was observed in the group with duodenal ulcers (89%) and the lowest in the group with oesophagitis (40%), and when antibody levels were compared (Fig. 2) the oesophagitis group had significantly lower levels (179 ± 94 antibody units, P = 0.034, Mann-Whitney test) than patients with gastroduodenal disease (666 ± 104).

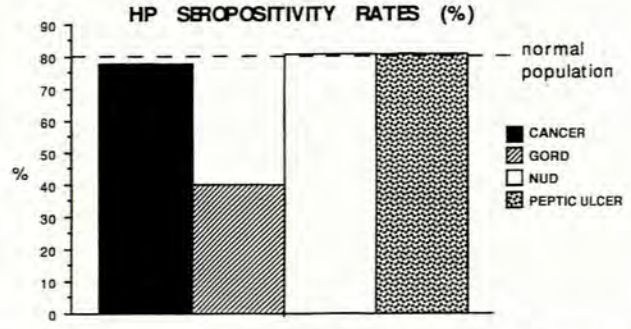

Fig. 1. HP seropositivity rates in the dyspepsia subgroups identified by endoscopic investigation compared with the rate found by Sitas et al.[17] *in the background 'normal' population, showing similar infection rates in black Africans with and without gastroduodenal disease.*

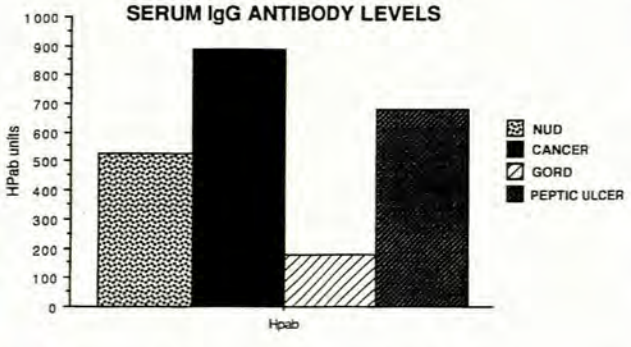

Fig. 2. Serum HP IgG antibody levels in the different subgroups of black African dyspeptic patients identified by endoscopic investigation. Levels were significantly lower in the group with distal oesophagitis (P < 0.05 Mann-Whitney test).

Only 5 of the patients with oesophageal cancer (i.e. 63%) were HP-seropositive. Their HP antibody levels (440 ± 162) were, on average, lower than those of patients with gastroduodenal disease (666 ± 104), but the difference was not statistically significant. Only 2 of the 5 patients with distal oesophagitis were serologically positive for HP, and as stated above, levels were significantly lower than those of patients with histologically confirmed gastroduodenal disease. The serological level was mildly positive (153) in the patient with antral dysplasia.

Evaluation of the potential therapeutic value of empiric anti-HP therapy

Overall, 78 patients (i.e. 80%) were HP-seropositive. Of these, 14 had 'alarm' signs and 9 were taking a NSAID. Consequently, 55 patients with 'simple dyspepsia' would have been eligible for empiric anti-HP therapy according to the decision analysis model proposed by Ofman *et al.*[10] Endoscopic evaluation indicated that this approach would have been effective in approximately 27 of the 55 patients, i.e. all the patients with peptic ulcers (8 duodenal ulcers (DUs), 1 gastric ulcer (GU)), and 45% of the 41 with non-ulcer dyspepsia. The treatment would, however, have been inappropriate in 3 patients presenting with simple dyspepsia but without dysphagia, who were found to have early oesophageal cancers, and in 1 with distal oesophagitis.

Of the 19 patients who were seronegative, 4 had 'alarm' signs and 1 was taking NSAIDs, leaving 14 with uncomplicated dyspepsia who would have been eligible for empiric antisecretory therapy.[16] Endoscopy indicated that symptomatic response would have been expected in the 2 patients with peptic ulcers (1 DU, 1 GU), in the 2 with distal oesophagitis, and in approximately half the remainder with non-ulcer dyspepsia (4 microscopic gastritis, 5 histologically normal). Importantly, no patients with malignant disease were identified in this group. Consequently, the use of empiric antisecretory drugs in HP-negative patients with uncomplicated dyspepsia could be expected to produce a symptomatic response in 61%, without missing patients with cancer.

If the analysis was restricted to patients under the age of 45 years, then HP antibody levels would again fail to predict the presence of peptic ulceration (PUD 567 ± 246 v. NUD 463 ± 117). However, empiric treatment would not have resulted in delayed diagnosis of cancer, although 1 case of oesophageal dysplasia would have been missed. A negative test in a patient aged under 45 may prove more useful, as all patients with peptic ulcers were serologically positive.

Discussion

Our results indicate that serological testing for HP in black Africans with upper gastro-intestinal symptoms is neither

helpful in predicting the presence of underlying upper gastrointestinal disease nor useful in planning treatment and management. For example, HP positivity was similar in patients with peptic ulcers and in those with non-ulcer dyspepsia. Unlike the situation in the developed world, empiric treatment of HP-positive dyspeptic patients without endoscopy would have led to the overuse of antibiotics, as nearly all patients were infected, and delay in the diagnosis of early cancer. The only possible use for the test would be to identify the relatively small group of non-infected patients with uncomplicated dyspepsia (i.e. 14%), who, in this study, were found not to have cancer and who might have benefited from simple antisecretory medications. Although 2 patients with oesophageal cancer were HP-negative, they had 'alarm' symptoms (weight loss and dysphagia) and early endoscopy would have been indicated.

The explanation for the lack of discriminant function of HP serology is probably related to the high background infection rate in the 'normal' population. For example, a recent survey based on a random sample of 986 black South Africans from the Cape Province aged 15 - 64 years found an overall seropositivity rate of 86.4%, with no age-related differences.[17] Infection appears to increase progressively during the first decade of life to a plateau adult rate of over 80%. This was well illustrated by a survey of groups of 100 children from the same region as our study, which found that 30% of 0.25 - 2-year-olds, 48.5% of 2 - 5-year-olds, 67% of 5 - 10-year-olds, and 84.2% of 10 - 15-year-olds were HP-positive.[18] The latter survey also found that seropositivity failed to distinguish between children with and without abdominal complaints.

It is clear, therefore, that chronic HP infection is the *usual* finding in black Africans. The question then arises — does the infection adversely affect their general health? The chief concern about long-term exposure to HP is the risk of gastric neoplastic change, either to carcinoma or lymphoma.[4,5] There is considerable experimental and epidemiological evidence to support the conclusion of the International Agency for Research on Cancer at the World Health Organisation that the organism is a Group 1 carcinogen.[6] Huang *et al.*[19] recently reported the results of their meta-analysis of all suitable published cohort or case-control studies on the subject, and concluded that the average odds ratio for HP-positive individuals developing cancer was 1.92; ranging from 9.29 in 20 - 29-year-olds to 1.05 in > 70-year-olds. However, although they included studies from the USA, Europe and the Far East, no studies from Africa met the entry criteria. This was unfortunate, as there is circumstantial evidence that the inclusion of African data would weaken the association. Holcombe[12] was the first to document that the prevalence of gastric cancer, and peptic ulcer disease, was not higher in black Africans, despite the ubiquitous nature of the infection in the community.[12] The National Cancer Registry in South Africa reports that the incidence of gastric cancer in 1992 among black South Africans was lower (3.5/100 000 for males, 2.2/100 000 for females) than the rate among whites (10.3/100 000 males, 5.5/100 000 females), whose HP positivity was lower (40%).[20,21] Our survey identified 1 dyspeptic patient with gastric cancer, a detection rate similar to that found in endoscopic surveys in communities with lower HP prevalence.[22,23] Additionally, histological proof of atrophic gastritis, the considered precursor lesion for carcinoma, was not found, although 1 HP-positive patient was shown to have antral dysplasia.

The prevalence of peptic ulcer disease is also no more common in South African blacks; in fact it is probably less common than in Western communities. Hospital admissions for complicated ulcer disease are rare, and in the early days of endoscopy, Moshal *et al.*[24] found peptic ulcer disease to be less frequent in blacks than in white or Asian South Africans. Again, the frequency of peptic ulcer disease in our black dyspeptic patients was no greater than the incidence reported in similar Western studies.[22,23]

The explanation for the 'African enigma', as it has been termed,[12] remains unclear. It seems unlikely that host genetic factors are responsible, as African-Americans do not have a lower prevalence of disease than Caucasian-Americans (in fact, ulceration and cancer are more common[25]). Consequently, other environmental factors and organism virulence probably account for the differences. A preliminary study[26] reported a lower occurrence of virulent vac-A-positive organisms. However, ulcer recurrence is reduced to the same degree in Africans following HP eradication,[27] indicating the presence of organisms with similar pathological properties in the community. Age of initial infection may also play a role as it has been suggested that infection in childhood reduces the likelihood of complications.[28] It would be surprising if diet was protective as the African diet is notoriously poor in quality, and depleted of antioxidant vitamins.[29] However, the diet may contain as yet unrecognised protective factors, as it differs greatly from the diet consumed by Western populations, consisting chiefly of low-protein, high-carbohydrate boiled cornmeal.[30] Gastric acid is also an unlikely contender as secretion is, if anything, low, owing to genetic and environmental factors (e.g. chronic malnutrition).[31]

Of greater immediate concern is the high prevalence of oesophageal cancer among Africans. Although this has been recognised for many years, theories on aetiology remain inconclusive. Prevalence rates are high throughout rural communities, but geographical clustering is evident — as in the area of the Transkei and Ciskei where the present study was conducted. This has suggested that infective or micronutrient factors may be responsible, and associations have been drawn with infections such as the human papillomavirus,[32] fungal contamination of stored corn,[33] and an impoverished diet lacking in protein and vitamins.[34] As the disease is usually detected late owing to the lack of endoscopic screening facilities, management is generally supportive, with dilatation

or stent placement, and early mortality is universal. Our study shows that mobile endoscopy, with biopsy and brush cytology, could help to identify risk factors such as precursor epithelial aberrations, dysplasia and human papillomavirus infections, as well as early treatable cancers. Simple brush cytology has also been proposed, whereby subjects swallow a gelatin-coated brush attached to a string. Although initial reports were encouraging,[35] the technique has never been implemented for population screening because of problems of manpower and compliance. From the results of our study it seems unlikely that HP plays a significant role in the disease as there was no useful association between serological results and oesophageal cancer — in fact 2 cases were HP-negative.

There has been concern that HP infection may increase the risk of enteric infections in the community,[36] as infection with virulent organisms suppresses gastric acid secretion.[37] Should this be the case, we might expect nutrition to suffer, and yet neither in our study, nor in the survey of children mentioned earlier,[18] was there any difference in the nutritional status of HP-positive and -negative individuals. In fact, protein-energy malnutrition was more common in HP-negative children (27% v. 19%). As a general index of health, we could find no lowering of haemoglobin concentrations in HP-positive dyspeptic patients.

Finally, there is emerging evidence that there might even be beneficial aspects of chronic HP infection. Blaser[14] has recently argued that as the organism has been with us for millions of years, it may confer currently unrecognised survival advantages. While this aspect is only beginning to be looked at, there is already concern that eradication may promote gastro-oesophageal reflux[13] and Barrett's oesophagus, and that it may increase the risk of proximal gastric and lower segment oesophageal adenocarcinoma.[38] The recognition that the progressive decline in HP infection in the USA this century has been accompanied by a steady increase in gastro-oesophageal reflux disease (GORD), Barrett's oesophagus, and a five-fold increase in adenocarcinoma of the distal oesophagus, supports the proposal that HP, or certain strains of HP, may have protective gastro-intestinal effects. In an attempt to explain this observation, Richter *et al.*[39] have suggested that it is the loss of virulent cagA-positive HP strains that has resulted in the disinhibition of gastric acid secretion, with potentiation of acid-reflux damage to the gastro-oesophageal region.[39] Based on these concerns, the investigations called for a critical re-evaluation of our approach to worldwide elimination of the organism, and even went as far as suggesting that inoculation with 'good' strains may prove effective in reversing the increasing prevalence. From the African perspective, the high rate of HP infection may well account for the low prevalence of GORD, Barrett's oesophagus and junctional adenocarcinoma. It would also explain our finding of lower HP seropositivity rates and antibody levels in patients with oesophagitis.

It is therefore reasonable to conclude that efforts to reduce the risk of cancer of the oesophagus are more crucial to the health of black African communities than efforts to remove HP infection. Strategies should include a general improvement of the diet and early detection of oesophageal dysplasia, rather than a policy of HP containment by vaccination or eradication with antibodies. Broad-spectrum antibiotic therapy not only runs the risk of inducing antibiotic resistance within the community, but more importantly it may disturb the normal gut ecology, which may be responsible for the inherent resistance of black African populations to other gastro-intestinal diseases, such as inflammatory bowel disease and colon cancer.[40]

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