

Commentary

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Helicobacter pylori—an African perspective

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Summary

Helicobacter pylori is ubiquitous in Africa, with acquisition in childhood the rule. Despite the prevalence of a virulent strain (in Soweto, most *H. pylori* organisms are *cagA*- and *vacAS*₁-positive) *H. pylori*-associated pathology (duodenal ulcer, gastric ulcer and gastric cancer) has a variable, often low distribution in sub-Saharan Africa that does not parallel *H. pylori* prevalence in the population, suggesting a different natural history from that seen in developed countries. Progression to atrophic gastritis in Africans does not appear

to differ from that reported in other regions, but as yet unidentified factors may play a role in inhibiting progression to gastric cancer. Studies have suggested that the specific IgG subclass response to *H. pylori* is predominately IgG₁ (suggestive of a Th2 response), and the Th2 response may provide a protective effect against development of gastric cancer. Host immune mechanisms may be the key to different responses to *H. pylori* in the developed and developing worlds.

Introduction

Since the discovery of the vital role that *Helicobacter pylori* plays in upper gastroduodenal disease, a ripple effect has been observed which has resulted in new insights into the impact of *H. pylori* on pathology and physiology of the stomach. Of interest in this respect is the 'African enigma'—a high prevalence of *H. pylori* with an apparently low incidence of gastric cancer.¹ We explored various aspects of this enigma, to better understand the background and role of *H. pylori* in gastroduodenal disease in Africa.

Helicobacter pylori infects more than half the world's population. The prevalence of the infection varies, however, both among countries and within different racial groups resident within

the same country. In both developed and developing countries, the highest rates of infection are associated with low socio-economic status, crowding, poor sanitation and unclean water supplies.²

In general, in developing countries >50% of children are infected by the age of 10 years, the prevalence of infection rising to >80% in young adults.³ In contrast in the majority of developed countries, children become infected at a rate of less than 1% a year.² Indeed, it is this significant difference in the rate of childhood acquisition of infection that is responsible for the differences in prevalence of *H. pylori* infection observed between developed and developing countries.²

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Epidemiology of *H. pylori* in sub-Saharan Africa

Serological studies conducted in different regions of Africa have shown that the majority of subjects are infected with *H. pylori*, 61–100% having antibodies to *H. pylori*.^{1,4} In the Ivory Coast, 55% of children aged <10 years have been reported to be infected, while in northern Nigeria and Gambia, 50% of children under 5 years are infected.¹ Studies in South Africa have shown acquisition at an early age. Indeed, South African children from Bloemfontein aged 0–1 year have been reported to have a seropositivity rate of 41%, although this rate may be an overestimate, as maternal antibodies were not considered.⁵ A recent study in Soweto found 46% of children at 1 year and 100% of children at 12 years to be infected with *H. pylori*.⁴

H. pylori-associated pathology in sub-Saharan Africa

Duodenal ulcer (DU)

Tovey and Tunstall⁶ have shown that there is a definite geographical pattern to the distribution of duodenal ulcer in sub-Saharan Africa, with a high incidence being reported in the Nile/Congo watershed and coastal regions of West Africa. High incidence rates of duodenal ulcer have also been reported in a number of major cities of Africa (Johannesburg,⁷ Durban,⁸ Nairobi⁶ and Mombasa⁶). In a recent study by Kidd *et al.*, 26% of patients with dyspepsia had DU, and of these *H. pylori* was present in 90%.⁹

Gastric ulcer (GU)

Gastric ulcer is uncommon in Africa, occurring 6–30 times less commonly than DU.⁶ In developed nations, the ratio of DU:GU is between 3:1 and 4:1.⁶ In Africa, a wide range of DU:GU ratios has been reported varying from 3:1 to 15–20:1.^{1,7,10} A retrospective endoscopic review of dyspeptic patients from 12 African countries found that 7% had GU, and that *H. pylori* was present in 75% of these patients.⁹

Gastric cancer

Gastric cancer has a generally low but variable incidence in Black populations of sub-Saharan Africa. Holcombe suggests that in the absence of accurate population statistics, the most useful indicator of tumour incidence is the proportional frequency of one tumour compared with that of

all other tumours.¹ Using this index, gastric cancer accounts for <2% of all malignant tumours in northern Nigeria, and only 2–3% of malignancies in the Sudan.¹ The mean rate in South Africa per 100 000 population is 2.6,¹¹ in Gambia 2.7,¹² Uganda 4.2,¹³ Mali 15.3¹² and Zimbabwe (Harare) 16.1.¹² Data on the incidence of gastric cancer show opposite trends in relative proportions in Ibadan (falling) and Bulawayo (rising).¹⁴ In Africa, in the majority of cases, cancers were reported to be located in the gastric antrum, were of the intestinal type and occurred in patients aged >50 years.^{15–20} The male:female ratio is 2:1 in most parts of Africa.

Our experience in Soweto supports the low incidence of gastric cancer in Black South Africans.¹¹ Hospital records from Chris Hani Baragwanath Hospital show that from 1948 to 1964, gastric cancer accounted for 2.2% of all cancers diagnosed, and in 1992 the figure was 2.8%, representing on average of 40 cases annually.²¹ Chris Hani Baragwanath Hospital, with 3200 beds, serves the population of Soweto which has grown from half a million people in 1940 to 3–4 million people in 1998.

Characteristics of *H. pylori* in Soweto

H. pylori possesses numerous virulence factors. Two well-characterized putative virulence determinants are the cytotoxin-associated gene (*cagA*) and the vacuolating cytotoxin gene (*vacA*). Studies in developed countries have shown disease specific-associations between infection with *cagA*-positive and specific *vacA*-positive strains of *H. pylori*.^{25,26} In particular, carriage of *cagA*-positive strains of *H. pylori* has been consistently associated with increased levels of inflammation. *cagA* is part of a large pathogenicity island, the *cagPAI*, which encodes a type IV secretion system.²⁷ This system permits the transfer of bacterial proteins into the host gastric mucosal epithelial cell, resulting in the transcription of pro-inflammatory cytokines such as IL-8, a molecule known to be responsible for the recruitment of neutrophils.^{28,29} Up-regulation of IL-8 is not associated with *cagA* directly, but has been associated with a number of genes within the *cagPAI*, in particular *cagE*.^{30,31}

In a Sowetan study of 89 asymptomatic children aged 6–15 years, 86.5% were infected with *H. pylori*; 61% of these children were infected with a *vacA*-positive strain of *H. pylori* and 87% with a *cagA*-positive strain.²² In addition, in a study of Sowetan adults, the majority of *cag*-positive

strains of *H. pylori* carried the *vacAS*₁ allele of the *vac* gene, while most *cag*-negative strains carried the *vacAS*₂ allele.^{23,24} The DNA sequence motifs at the right end of the *cagPAI* are similar in Sowetans to those seen in the US and Europe.³²

Discussion

H. pylori is ubiquitous in Africa, with acquisition in childhood the rule. Most Sowetans studied have a virulent organism. *H. pylori*-associated pathology (DU, GU and gastric cancer) has a variable distribution in Africa which does not parallel the prevalence of *H. pylori* in the population.

It has been suggested that prospective endoscopic studies might reveal a higher prevalence of *H. pylori*-associated disease in Africa.⁹ However, if this were the sole explanation, then in Africa a high prevalence of *H. pylori* should be accompanied by a high level of *H. pylori*-associated disease. This does not seem to be the case in (e.g.) Soweto, where the prevalence of gastric cancer is consistently low.

The following arguments have been advanced to explain the 'African enigma'.

(i) Patients may not present to hospital with carcinoma of the stomach. However, people with other high incidence cancers such as oesophageal and cervix cancer seek help from hospitals; why then should people with gastric cancer not report?

(ii) There is no denying that in symptomatic patients a cancer incidence of 2.3% may be observed. However, this is a skewed figure, as it represents only symptomatic people and not the vast majority of people harbouring *H. pylori* who are asymptomatic.

(iii) Average life expectancy in sub-Saharan Africa is much lower than in industrialized countries. However, the life expectancy in Black South Africans has been reported to be 63 years³³ (prior to the AIDS epidemic). Given that *H. pylori* acquisition occurs in early childhood, it would be expected that in many patients gastric cancer would present before 60 years of age.

(iv) In many Africans, *H. pylori* seems to have a different natural history than in developed countries. In a review article, Kuipers and Meijer³³ have suggested that the progression to atrophic gastritis in the African population does not differ from that reported in other regions, but that yet unidentified factors may play a role in inhibiting progression to gastric cancer.

(v) The immune response to infectious agents leads to the expansion of particular CD4+ve T-helper (Th) cell subsets. Th1 cells are reported to produce Interleukin (IL)-2, IL-12 and interferon γ (IFN γ), and are associated with cell-mediated

immunity, while Th2 cells have been reported to secrete IL-4, IL-5, IL-6, IL-10 and IL-13, and are responsible for strong antibody responses, including IgE-dependent allergies of the immediate type.³⁴ In general, Th1 responses are associated with intracellular micro-organisms including bacteria, protozoa and fungi, whereas extracellular pathogens induce Th2 responses. Studies to date have shown that natural infection with *H. pylori*, which is by and large an extracellular infection, leads to a Th1-predominant response, with IL-2, IL-12, TNF α and IFN γ reported to be present in the gastric mucosa of *H. pylori*-positive subjects.³⁵⁻³⁷ In contrast, the Th2 cytokines IL-4 and IL-5 have been found to be virtually absent in *H. pylori* infected subjects although a number of studies have reported IL-10 to be present in the gastric mucosa of subjects with *H. pylori*-related active gastritis.^{35,37,38}

Recently, Fox *et al.*³⁹ have provided evidence for a possible explanation for the 'African enigma'. They showed that mice infected with *Helicobacter felis* alone showed a Th1 response, but in mice co-infected with *H. felis* and the helminth *H. polygyrus*, there was a shift to a pattern of cytokine expression consistent with a Th2 immune response. This corresponded to a significant reduction in mucosal hyperplasia, mucosal metaplasia and glandular atrophy. Thus, associated with the Th2 immune response, there was a marked reduction in *Helicobacter*-associated corpus atrophy, despite chronic inflammation and high *Helicobacter* colonization. If this is extrapolated to man, then intestinal helminth infection may provide a protective effect against development of gastric atrophy and gastric cancer.

Given that animal models do not necessarily replicate the human situation, Fox's study and Kuiper's study, although in some respects contradictory, indicate the complexity of biological actions associated with *H. pylori*.

In a recent study, Mitchell *et al.*⁴⁰ measured the IgG subclass antibody response to *H. pylori*, considered to be a biomarker of the T helper cell response, in Sowetan, German and Australian *H. pylori*-positive subjects. In Sowetans, the specific IgG subclass response to *H. pylori* was shown to be predominately IgG₁ (suggestive of a Th2 response) whereas that in the Australian and German population was predominately IgG₂ subclass (suggestive of a Th1 response). Interestingly, in a study by Ally *et al.*⁴¹ to determine the total IgE antibody levels (surrogate marker for parasitic infection) in Sowetan adults and children, a high percentage of subjects had total IgE and total IgG₁/G₂ levels above the normal range. These findings suggest that the prevalence of previous gastrointestinal parasitic infection in Sowetans is high, a finding that may

explain the different immune responses to *H. pylori* in this community.

McCull *et al.*⁴² have postulated that acute infection and/or inflammation of the antrum stimulates increased release of gastrin (a consequence of depletion of somatostatin). This increased gastrin stimulates the parietal cells to secrete excess acid. The degree of increased acid released is dependent on the parietal cell mass. The resulting increased duodenal acid load leads to the development of gastric metaplasia and eventually ulceration. In patients who develop gastric ulcer or gastric cancer, the infection and gastritis involves the acid-secreting body mucosa, and is associated with mucosal atrophy. The inflammation and atrophy of the acid secreting body mucosa results in hypochlorhydria or achlorhydria. El Omar *et al.*⁴³ suggest that host genetic factors that affect interleukin 1-beta (a powerful inhibitor of gastric acid secretion) may determine why some individuals infected with *H. pylori* develop gastric cancer and other do not.

The situation in Africa also highlights other current controversial issues. It has been suggested that *H. pylori* in most people is harmless and may have potential benefits.⁴⁴ Indeed, the organism may be protective against the development of gastro-oesophageal reflux and its complications.⁴⁵ Data indicate that hiatus hernia, gastro-oesophageal reflux, Barrett's oesophagus and adenocarcinoma of the oesophagus are all rare or uncommon in Black Africans.⁴⁶⁻⁵² The rationale for this protection is that *H. pylori* gastritis affecting the corpus may produce a gastritis severe enough to cause a major reduction of gastric acid secretion⁴⁵ and a substantial elevation of gastric pH, compared to subjects who are not *H. pylori*-infected. As a corollary, the decreasing rate of *H. pylori* in developed countries will result in a more effective preservation of acid secretion into old age, with a consequent greater prevalence of reflux oesophagitis and its complications.⁴⁵

Conclusion

H. pylori infection is ubiquitous in Africa and acquired in childhood, yet complications associated with the bacterium are variable, unpredictable and particularly with regard to gastric cancer, generally low. The reasons for this inconsistency are unknown. A suggestion is that immune mechanisms play an inhibitory role. Paradoxically, *H. pylori* infection may be protective against gastro-oesophageal reflux and its complications. The hypothesis can be tested by further studies which investigate the correlation of *H. pylori* status with

the topographic extent and severity of gastritis, and the occurrence of reflux disease.⁴⁵ Positive results would call into question the policy of global eradication of *H. pylori*.

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