REVIEW ARTICLE

An African perspective of *Helicobacter pylori* infection: A narrative review

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ABSTRACT

Background: There is a high prevalence of *Helicobacter pylori* (*H. pylori*) infection in Africa, but data on its clinical presentation are limited. The African enigma, states that despite a high prevalence of *H. pylori* infection on the continent, related gastrointestinal diseases such as peptic ulceration and gastric cancer are not common. However, this conclusion was based on limited scientific evidence and has been challenged by some scientists.

Methods: This narrative review highlights gaps on our understanding of *H. pylori* infection in Africa, that limit the possibility of formulating evidence-based guidelines.

Results: We demonstrate a lack of understanding about the epidemiology of *H. pylori*-related gastric diseases such as peptic ulceration and gastric cancer. In addition, we discuss challenges related to drug resistance.

Conclusions: There is an urgent need to provide scientific evidence for the African enigma which will deepen our understanding of *H. pylori* infection on the continent. In addition, efforts at streamlining approaches to evidence-based eradication therapy need to be intensified.

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral bacterium found in the epithelial lining of the stomach of humans. It infects more than half of the world's population with a global prevalence of approximately 43.1 %[1,2]. Data on population-based epidemiology of *H. pylori* infection in Africa are scanty with an estimated prevalence of more than 70%[3]. Within the African continent, there is evidence of country-

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to-country variations, limiting the generalisability of current data[4].

Despite the high burden of *H. pylori* infection in Africa, there are a limited number of studies from the continent. Most information on *H. pylori* pathogenesis comes from outside Africa. In addition, there are very few evidence-based African guidelines on *H. pylori* treatment. but limitations on the applicability of existing international guidelines are evident[5]. Over 30 years ago, Holcombe proposed the 'African enigma', which stated that despite a high prevalence of *H. pylori* infection on the continent, related gastrointestinal (GI) diseases such as peptic ulceration and gastric cancer were not common[6]. However, the enigma was not based on clear scientific evidence and some scientists have disputed its validity, referring to it as a medical myth[7]. We now know that limitations of case ascertainment of *H. pylori*-related GI diseases, makes it difficult to determine the exact prevalence of these conditions, as many are diagnosed endoscopically. Endoscopy services are very limited in Africa, and in many places concentrated in large cities[8].

In this narrative review, we present an African perspective to current understanding of *H. pylori* infection, highlighting the transmission, diagnosis and treatment. To collect data for this review, we conducted literature searches in PubMed and Google Scholar. We used key words including; Africa, *Helicobacter pylori*, drug resistance, antibiotics, prevalence, diagnosis, mechanism, eradication, therapy, and enigma in various combinations to retrieve relevant articles. These articles were then summarised, synthesised and integrated into the write up.

EPIDEMIOLOGY OF *H. PYLORI* IN AFRICA

Africa has one of the highest prevalence of *H. pylori* in the world, but there are few countries that have reported accurate population-based data. The exact mode of transmission for *H. pylori* is uncertain, but it is thought to be via faecal-oral, oral-oral and gastro-oral routes[9,10]. Faecal-oral transmission is thought to be the most common in developing countries owing to the poor standards of hygiene in most of these countries[11]. A study in Ghana showed strong epidemiologic association between *H. pylori* infection in children and lack of piped or borehole drinking water. In addition, they reported that open air defecation was practised by all the children who were found to be *H. pylori* positive[11]. Waterborne transmission of *H. pylori* is possibly an important source of infection in Africa, and improving hygiene and sanitation could help to reduce the rate of transmission[12,13].

It is currently believed that acquisition of *H. pylori* infection occurs in childhood and tends to remain asymptomatic until later in life[14]. Infection in children is believed to be more common in developing countries with high prevalance rates of 63.6 to 85.1% although there are some variations with some reported rates as low as 30%[15-17]. Lack of proper sanitation as well as overcrowding (both of which are common in Africa) increase the risk of children acquiring the infection from adults[15,18].

MECHANISM OF *H. PYLORI* INFECTION

H. pylori thrives in the acidic, aerophilic environment of the gastric mucosa by producing large quantities of the enzyme urease[19]. Urease hydrolyses urea into ammonia

(NH_3) and carbon dioxide (CO_2) and the presence of these compounds in large amounts results in generation of a pH-neutral microenvironment, allowing the *H. pylori* to grow in abundance[20,21].

The infective ability of *H. pylori* is heightened by its mobility, adherence and manipulation of the gastric microenvironment. These mechanisms improve its capacity to colonize the stomach lining. *H. pylori* has about 4-8 flagella, measuring 30 nm in diameter and 12-15 nm in length[22]. Flagellar filaments, FlaA and FlaB, play an important role in motility and pathogenesis[23].

Various outer membrane proteins encoded by virulent genes work to enable persistent occupation of the gastric mucosa. The effects of *H. pylori* such as vacuolation, rearrangement of the cytoskeleton and delayed phagocytosis are as a result of the virulence factors[24, 25]. The two well studied virulence factors which have been widely associated with peptic ulceration and gastric cancer are cytotoxin-associated gene A (*CagA*) and vacuolating cytotoxin A (*VacA*). *CagA* has been shown to play a key role in the development of *H. pylori*-associated gastritis and gastric cancer. When *CagA* is introduced into the host cell, it alters the cytoskeletal structure and cell proliferation. *CagA*-positive *H. pylori* strains can induce apoptosis in the host epithelial cells which reduces the integrity of the gastric epithelium[25,26]. This predisposes to development of mucosal lesions. *VacA* induces the formation of vacuoles and has been shown to interfere with endosomal vesicular trafficking[27,28]. *VacA*-positive strains can further be defined by the subtype which are based on the genotypes. Data on *VacA* mosaicism in African strains are limited, but a recent study demonstrated significant differences between South African and Nigerian isolates . In this study 82.9 % of Nigerian isolates haboured an s1m1 region compared to lower frequency of 62.3 % in South African isolates[29]. There were also differences in frequency of s1m2 and s2m2 between the countries with some isolates not fitting into the m- or s- region subtytpes. No significant difference was observed in the vacuolating cytotoxicty of the African s1m1 phenotypes compared to European strains however additinal studies are required to study the cytocity of the other phenotypes[29].

There are some inconsistencies of data supporting the role of *CagA* and *VacA* virulence factors in Africa[30]. A recent study from Zambia utilising *H. pylori* multiplex panel, found that *Cag A* and *VacA* were associated with acute gastritis but not gastric cancer or its premalignant lesions[31]. This is line with an earlier study that showed no association between *H. pylori* serology with gastric cancer in Zambian patients[32]. However, other studies have demonstrated the role for these virulence factors in *H. pylori*-associated disease conditions in Africa[33,34]. There is need for more research to streamline the role of *Cag A* and VacA in disease occurrence within the African continent in order to understand the complex interaction of the gastric environment and host responses as the presence of these virulent genes is thought to play a vital role in disease progression and severity of outcome.

CLINCAL SYMPTOMS OF *H. PYLORI* IN AFRICA

Much of the pathology associated with *H. pylori* infection is a result of the persistent immune response which drives development of associated disease conditions. *H. pylori*

infection primarily affects the stomach and duodenum causing gastritis or duodenitis which can be confirmed histologically by the presence of inflammatory cells within the mucosa. In about 20% of the cases, *H. pylori* infection causes peptic ulceration, resulting in upper GI symptoms such as epigastric pain associated with food intake. The majority of affected individual therefore do not have any symtoms. It should be noted here that the use of non steroid anti-inflammatory drugs (NSAIDs)is also associated with peptic ulceration. The complex interplay bewteen NSAIDs and *H. pylori*has been well studied with reports indicating that NSAIDs augment *H. pylori* infection and some sugesstion that there is a lower incidence of *H. pylori* in patients taking NSAIDs[36-38].

It was previously thought that peptic ulceration was uncommon in Africa, but with improved diagnostic capabilities, it is becoming apparent (at least in some African countries) that peptic ulceration is prevalent[39]. In a community-based endoscopic study from Zambia, the prevalence of gastroduodenal pathology in *H. pylori*-infected individuals were similar to that reported from western countries[40]. This provided evidence against the validity of the African enigma.

Individuals with *H. pylori*-induced chronic active gastritis can eventually start losing gastric glandular tissue, leading to atrophic gastritis[41]. Atrophic gastritis may progress to intestinal metaplasia (IM) in which the gastric columnar epithelium is replaced by intestinal-type epithelium. IM can be either morphologically similar to the small intestines (complete type) or the colon (incomplete type). The incomplete type has greater propensity to advance to a more disorganised mucosal tissue, in a condition called dysplasia. Dysplasia can then develop into gastric cancer (intestinal type gastric adenocarcinoma). This process of advancing from chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and cancer is called the Correa pathway of gastric carcinogenesis[42]. Similar to peptic ulcers, recent data have shown that the prevalence of IM in Africa is no lower than elsewhere. For example the reported prevalence of IM was 17 % in Zambia, compared to 13.8 % in Turkey, 13.7 % and 11.9 % in American non-Hispanic white patients and African Americans respectively providing further evidence against the African enigma[32,43,44].

H. pylori is a class 1 carcinogen with gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue lymphoma being direct consequences of chronic untreated *H. pylori* infection[45]. It is currently thought that the occurrence of these conditions is low in Africa, which would be in support of the African enigma. There is an urgent need to accurately determine the incidence of gastric cancer in Africa as that will provide clear evidence for or against the African enigma.

DIAGNOSIS OF *H. PYLORI* IN AFRICA

There are several modalities available for the diagnosis of *H. pylori* infection. These are of varying specificity and sensitivity depending on the sample being used, mode of collection, burden of colonisation and in some cases, drugs being taken at the time of running the tests. *H. pylori* can be diagnosed using non-invasive methods (breath test, stool antigen test or serology) and invasive tests that involve endoscopic collection of biopsies for rapid urease testing, bacterial culture or molecular testing such as real-time PCR, digital PCR and whole genome sequencing[46].

The rapid urease test is the most commonly used technique, globally, for *H. pylori* diagnosis. It is based on the principle that *H. pylori* possesses urease which facilitates the hydrolysis of urea, producing ammonia and carbon dioxide. The ammonia alkalinises the medium resulting in a pH increase detected by colour change of phenol red from light orange to magenta. This test uses endoscopically obtained biopsies which is not easily feasible in most African settings. Immunochromatographic tests have also been used to detect the sero-prevalence of *H. pylori* antibodies and the presence of *H. pylori* antigens in stool samples[47]. With the high prevalence of *H. pylori* infection in Africa, serological detection of antibodies is of very limited clinical utility as it does not provide information on disease activity. Stool antigen testing is relatively cheaper and is available in many African settings. The stool antigen test would be the most practical to advocate for in Africa as it can also be used to test for successful eradication. Urea Breath testing is not available in most centres in Africa. It utilizes the ability of bacteria to degenerate C^{13} and C^{14} labelled urea into carbon dioxide (CO_2). A study was conducted in Brazil to test a cost-effective method of production of this test. It showed positive results which might merit repetition in other developing countries[48].

Advances in genetic screening have enabled the identification of regional strains of *H. pylori*. Multi Locus Sequence Typing identified hpNEAfrica, hpAfrica1 and hpAfrica2 lineages of *H. pylori* in Africa. The hpAfrica1 lineage was further subdivided into the hspWAfrica, hspSAfrica and hspCAfrica subpopulations[49]. Both environmental and genetic factors are believed to contribute to the emergence of the different *H. pylori* strains[50]. Prevalence of identified isolates in Africa has not been thoroughly studied, which may be attributed to the cost of running these tests. Therefore, the diagnosis of *H. pylori* infection is still quite a challenge in many regions of Africa. However, it does emphasize the need to characterize strains that are responsible for infection as this could be where the difference in infection outcome lies.

EVIDENCE-BASED TREATMENT FOR *H. PYLORI* IN AFRICA

H. pylori treatment is given to not only cure existing associated diseases such as peptic ulceration, but to also prevent the development of gastric cancer. *H. pylori* eradication has shown to greatly influence the prevalence of gastric cancer. *H. pylori,* when present in the stomach, causes gastritis, and is therefore considered an infectious disease[35]. Many experts advise that all infected individuals should be given eradication therapy[35,47,51]. However, in Africa some believe that if associated GI illnesses are uncommon then mass *H. pylori* eradication could lead to unnecessary antimicrobial resistance and cost. Thus, a better understanding of the extent of *H. pylori* associated illnesses is essential.

To eradicate *H. pylori* infection, antimicrobials known to be potent against the infection are used. In addition, there is need for gastric acid suppression which enhances clearance of the bacteria.

TREATMENT REGIMENS FOR *H. PYLORI*

Triple and quadruple therapies

According to the Maastricht VI/Florence consensus report, when resistance to clarithromycin is less than 15%, the first line

regime for *H. pylori* treatment can be either clarithromycin triple therapy which includes a proton pump inhibitor (PPI), clarithromycin and amoxicillin or metronidazole and alternatively bismuth quadruple therapy (PPI, bismuth, tetracycline and metronidazole). As second line, levofloxacin triple or quadruple can be used depending on the combinations included as first line. When clarithromycin resistance is 15% or more, bismuth quadruple therapy is the preferred first line with non-bismuth quadruple as the alterative[47]. Many biological and non-biological factors including antimicrobial strength, cost, side effects, duration of action, tolerability, local antibiotic use and bacterial resistance determine the effectiveness of antibiotics[52]. In addition, patient compliance, body weight, type of *H. pylori* strains, high bacterial load, gastric acidity and atrophic gastritis may also impact cure rates[53]. Because prior exposure to macrolides increases *H. pylori* resistance rates to clarithromycin, a review of patients' prior antibiotic use is important to increase cure rates[54,55].

Reports from some parts of the African continent have shown resistance to amoxicillin to be as high as 38% with metronidazole resistance being close to 92%. There are also reports of clarithromycin resistance being more than 15%, and therefore bismuth-based therapy could be the best option. However, bismuth is not readily available in many parts of the continent[5].

Sequential Therapy

Sequential therapy is a 10-day therapy comprising 5 days of a PPI plus amoxicillin followed by 5 days of triple therapy of a PPI, clarithromycin and metronidazole[57,58]. In patients with penicillin allergy or in areas with high clarithromycin resistance, levofloxacin can be used[59]. This regimen is considered an alternative to standard triple therapy in areas with high clarithromycin resistance although it includes clarithromycin itself[54,60]. To overcome clarithromycin resistance, this regimen employs the use of amoxicillin before clarithromycin. Amoxicillin disrupts *H. pylori* cell walls and prevents activation of efflux channels, one of the mechanisms of clarithromycin resistance[59,61]. Unfortunately, due to its complexity, this regimen results in decreased patient compliance. There is also a likelihood of developing multidrug resistance in case a patient fails treatment.

Concomitant Therapy

In this approach, a PPI, clarithromycin, amoxicillin and metronidazole are administered for at least 10 days. Compared to the standard triple therapy, this regimen has demonstrated superiority particularly in cases of clarithromycin resistance[62,63]. Concomitant therapy is advantageous due to its efficacy against dual antibiotic-resistant strains along with enhanced compliance compared to sequential therapy[63-66].

Hybrid Therapy

This regimen is a combination of sequential and concomitant therapies[67]. In this approach, dual therapy of a PPI and amoxicillin is administered for 7 days followed by addition of a concomitant quadruple therapy consisting of a PPI, amoxicillin, clarithromycin and metronidazole for a further 7 days. Eradication rates have been shown to be excellent even in dual clarithromycin- and metronidazole-resistant strains.

Quinolone-based Therapy

This second line treatment involves the administration of a PPI, levofloxacin and amoxicillin for 10 days. However, varying levels of eradication were reported in multiple studies conducted in mainly Europe and Taiwan which could perhaps indicate varying levels of levofloxacin resistance in the investigated populations[68]. A combination of levofloxacin, omeprazole, nitazoxanide and doxycycline administered for 7 or 10 days is another quinolone-based regimen which has been found to achieve higher rates of eradication compared to standard triple therapy[69]. After the patients have failed to achieve *H. pylori* eradication following standard first and second line therapies, levofloxacin-based therapies have also been considered in empiric third-line therapeutic regimens[70].

Rifabutin-based Therapy

A rifabutin-based therapy consisting of amoxicillin, a PPI and rifabutin has shown promising results as a salvage therapy for *H. pylori* eradication based on *in vitro* studies. Rifabutin is listed in guidelines for regions where bismuth and tetracycline are unavailable[71]. However, what remains uncertain for this anti-tuberculosis agent is the duration of treatment. Additionally, before rifabutin can be deployed widely, its rare myelotoxicity is an important complication that needs to be addressed[71]. Because its use could fuel mycobacterial resistance, the regimen should be reserved only for rescue treatment.

RECOMMENDATIONS

There is still much to learn about the ideal treatment therapies of *H. pylori* in Africa as it requires understanding the complexities of the interaction between *H. pylori* virulence factors, host immune responses and environmental factors which all contribute to the infection pathogenicity and treatment outcome. Antibiotic resistance is another important factor that influences the treatment outcome. International consensus recommends choosing the eradication regimen based on local resistance characteristics[47]. Application of current international guidelines is challenging in many African countries and not supported by local evidence[5]. Even though there are a number of small scale studies that have reported on *H. pylori* resistance and eradication rates, the studies differ in methodology, setting and there is a potential risk of bias as reports are normally origniating from only a handful of countries out of the 54 countries in Africa as evidenced by recent review attempts[56,72-74]. Therefore only few countries in Africa such as Egypt and Algeria have guidelines or recommendations on best *H. pylori* treatment options[75,76], and these do not apply to all the countries in Africa.

It is very clear that there are variable responses to current *H. pylori* treatment regimes in Africa[73] and our opinion is that with enhanced investment and support, locally generated data that is more applicable could be collected. Therefore there is need to encoruage more research on *H. pylori* in all African countries. Countries can be encouraged to collect information on prescribed regimes, compliance, treatment outcomes and antibiotic resistance on centralised plaftorms for easy monitoring and improved managment of emerging *H. pylori* resistance. Furthermore there is also need to develop capacity for antibiotic resistance screening and tailored treatments to minimize eradication failure rates which will reduce the malignant and nonmalignant burden of *H. pylori* in Africa.

CONCLUSION

There is a high prevalence of *H. pylori* infection in Africa, but limited evidence to support the lack of associated GI illnesses. Diagnostic tools remain limited in most African health facilities and low cost, accurate, point of care tests are needed. Uncertainties on the best treatment options on the continent need urgent attention.

STATEMENTS

Statement of Ethics

This was a review article, therefore no ethics approval was sought.

Conflict of Interest Statement

The authors have no conflicts of interest to declare

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EF, PMC, KZ and VK conceptualise the idea of writing this review. EF, PMC, KZ, KC, JR and VK all contributed to the write up and final approval of the review.

Data Availability Statement

There are no data associated with this manuscript

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