Review Paper

Current Global Perspectives on the Pharmacotherapy of *Helicobacter Pylori* Infection: Therapeutic Implications for Sub-saharan Africa

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ABSTRACT

Helicobacter pylori is associated with many clinical conditions including gastric and extra-gastric pathologies. Prevalence is high in most Sub-Saharan African countries where data is available. Its association with diseases is not fully established in the region. Due to emergence of antibiotic resistance, the conventional triple and quadruple therapies using proton pump inhibitors and antimicrobial agents are now obsolete. Many Western countries have revised their therapeutic guidelines with a common recommendation to determine prior patient exposure to antibiotics, determine local drug resistance patterns and eradication rates, use higher doses of proton pump inhibitors, and include bismuth sub-citrate if clarithromycin resistance is suspected. Sub-Saharan African countries lack data on these making it difficult to apply these recommendations. The countries in Sub-Saharan Africa need to recognize the growing clinical importance of *H. pylori* and initiate programs to determine its local epidemiology, drug resistance, and its association with diseases in the region. Collaborative effort is required to achieve these goals and establishment of regional reference laboratories for monitoring drug resistance may be helpful.

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INTRODUCTION

Helicobacter pylori, a gram-negative organism that infects the gastric mucosa, is associated with several gut disorders such as peptic ulcer disease, chronic gastritis, and gastric cancers[1-5]. Its discovery led to dramatic changes in the management of peptic ulcer disease globally, and many countries recorded significant decreases in peptic ulcer incidence[6]. The records notwithstanding, in many developing countries, the prevalence of *Helicobacter pylori* infection remains high, while the actual values in most Sub-Saharan African countries are unknown. Available data from some of the African countries indicate very high prevalence values[7, 8]. To a large extent, this infection is neglected in the region[9], and the extent of its contribution to diseases in Africa is not clear.

Helicobacter pylori infection is commonly managed with a combination of antibiotics and gastric acid lowering drugs. Therapeutic guidelines in most countries recommend either triple therapy using two antibiotics plus a proton pump inhibitor such as omeprazole or two antibiotics plus H_2-receptor blocker such as ranitidine and cimetidine. Quadruple therapy involving the use of three antimicrobials and an acid reducing agent may be used in cases of failure with triple therapy. However, the effectiveness of these regimens is complicated by the emergence of drug resistance to most recommended antibiotics[10-14]. To this effect, most regions of the world, apart from Sub-Saharan Africa,

Key Words: *Antibiotic resistance, global perspectives, H. pylori, prevalence, Sub-Saharan Africa, therapeutic guidelines*

have revised their treatment guidelines for *H. pylori* associated diseases. The objectives of this article are to present the current global perspectives on *H. pylori* treatment in the presence of emerging antibiotic resistance, and to highlight the issues and challenges associated with the pharmacotherapy of *H. pylori* in Africa.

EPIDEMIOLOGY

The global prevalence of *H. pylori* infections is estimated to be more than 50 %[15-17]. There exists great disparity in regional prevalence however[18], with the advanced countries such as Switzerland and Denmark having values below 30 % while developing countries like Pakistan, Nepal, and Libya have values exceeding 75 %[15]. Countries in Oceania (such as Australia and New Zealand) appear to have the least prevalence values. Significant intra-regional variations also occur. Sub-Saharan African countries have the greatest burden of *H. pylori* infections, with many countries recording prevalence values higher than 70 %. For example, reported prevalence for the Republic of South Africa range from 51 % to 77.6 %[15, 19], Nigeria 83 % – 92 %, Benin 70 % – 81 %, and Democratic Republic of the Congo 70 % – 81 %[15]. Eusebi and others[20] recently presented a comprehensive review of the global prevalence of *H. pylori* infections.

Most *H. pylori* infections are acquired in childhood[21]. The social determinants of this infection are similar to those associated with other neglected tropical diseases and other endemic diseases of poverty. These include poor personal and environmental hygiene, poor drinking water quality, and overcrowded accommodation[22]. The precise routes of disease transmission are not certain, but evidence suggests that acquisition is usually via the oral-oral or fecal-oral transmission, drinking water and often perpetuates within the family circle[23-27].

Although *H. pylori* infection has ostensibly been identified as risk factor for gastro-duodenal ulcer, chronic gastritis, and gastric cancer, the association between these disease and *H. pylori* infection is unpredictable: only a small proportion of *H. pylori* infected individuals develop disease, and manifestation of disease as a result of infection appears to be determined by multiple factors including a geographical component[28-33]. For example, Aitila and colleagues[22] studied children with gastrointestinal complaints in Western Uganda and observed a *H. pylori* prevalence of 23.4 % compared to 44.3 % in another similar study in the general population in Kampala. The phenomenon initially described as the "African enigma," whereby seropositivity does not correlate with disease burden, has now been observed in other areas of the world[34-37]. This has been attributed to existence of strain to strain variation in the presence of certain pathogenicity factors.

PATHOGENICITY

The current knowledge of the spectrum of diseases caused by *H. pylori* infection has expanded. Emerging evidence shows that, in addition to well established association between *H. Pylori* infection and gastrointestinal diseases such as chronic gastritis and duodenitis, gastric and duodenal ulcers, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[38, 39], *H. pylori* is now known to be associated with several extra-gastric diseases such as cardiovascular, respiratory, neural, autoimmune, and metabolic diseases[40-48]. Several articles present comprehensive reviews on this topic[49-52].

The pathogenicity of *H pylori* has been linked to the presence of two genes, *cagA* and *vacA*[53,55]. The *cagA* gene is a member of the *cag* pathogenicity island (PAI) which encodes the CagA protein responsible for induction of interleukins and nuclear factors associated with *H. pylori* induced diseases[3, 56, 57]. The *vacA* gene encodes the vacoulating cytotoxin, VacA. VacA also has strong association with *H. pylori* pathogenicity[58-60].

PHARMACOTHERAPY AND DRUG RESISTANCE

The conventional treatments for *H. pylori* infections comprise a proton pump inhibitor in combination with antibiotics. Most guidelines recommend triple therapy with Clarithromycin, metronidazole, and/or amoxicillin, with a proton pump inhibitor as first line treatment. A quadruple therapy incorporating a fourth agent such as Bismuth compounds is also highly recommended in cases of therapeutic failure.

Reduction of gastric acidity is well accepted practice in the treatment of *H. pylori* infections. Not only is this desirable for the healing of any ulcers, but the higher gastric pH has been reported to reduce H. pylori load and increase the susceptibility of the organism to antibiotics[61]. The proton pump inhibitors take the lead in this respect and a higher dosage (twice daily) regiment is reported to be more effective than the standard (once daily) regiment. Recommended proton pump inhibitors include omeprazole (20 mg), rabeprazole (20 mg), lansoprazole (30 mg), esmoprazole (40 mg), and pantoprazole (40 mg). However, genetic differences may affect individual response to proton pump inhibitors[61], and chronic use of proton pump inhibitors is associated with risk of gastritis and gastric cancer[62-66]. Histamine (H_2) receptor blockers may be used as alternatives to proton pump inhibitors but their efficacy has been reported to be less than those of proton pump inhibitors[67]. Another class of gastric acid suppressants, potassium-competitive acid blockers exemplified by Vonoprazan, has been recommended as substitute to proton pump inhibitors for *H. pylori* treatment[68]. Vonoprazan (*1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine Monofumarate (TAK-438),* $C_{17}H_{16}FN_3O_2S$), competitively and reversibly block H+/K+ ATPase. Its efficacy in the treatment of *H. pylori* associated conditions is reported to equal those of proton pump inhibitors, but it has its own set of adverse effects[69].

Clarithromycin occupies a first-line position in the antimicrobial treatment of *H. pylori* infections. Triple or quadruple therapies that are clarithromycin-based have demonstrated high efficacies in the eradication of *H. pylori* infections, especially when metronidazole is included[70, 71].

However, the emergence of clarithromycin resistant *H. pylori* strains is now a global phenomenon that challenges the *a priori* established therapeutic guidelines for the clinical management *H. pylori* infections[72-74]. Resistance to other recommended antibiotics such as metronidazole, levofloxacin, and amoxicillin, are now commonly reported across the globe[75-77]. Bismuth subcitrate is increasingly recommended for inclusion as part of first line, second line, or rescue therapy in cases of demonstrated drug resistance and shows significant improvement in eradication rates[78-82].

The global emergence of *H. pylori* resistant strains has resulted in revisions of standard therapeutic guideline for its eradication. These modifications include the 'Kyoto Global Consensus on Helicobacter pylori gastritis' which presented comprehensive guide for the clinical management of *H. pylori* gastritis[83], the 'Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults'[84], and the 'Guidelines for the management of *Helicobacter pylori* infection in Italy: The III Working Group Consensus Report 2015'[85]. These consensus statements have many things in common which include the need to determine previous antibiotic exposure, knowledge of local/regional *H. pylori* drug resistance patterns and eradication rates, and the inclusion of bismuth sub-citrate in therapeutic regimens if clarithromycin resistance is suspected. The consensus statements also recommended using higher doses of proton pump inhibitors e.g. twice daily dosing instead of the usual once daily dosing and avoiding repeating the same regimen that failed. Table 1 presents a summary of these consensus statements.

Other therapeutic regimens have also emerged such as sequential and concomitant therapy[86]. In a typical sequential therapy, rabeprazole (a proton pump inhibitor) and amoxicillin were initially given for 5-7 days followed by rabeprazole, clarithromycin and metronidazole for a further 5-7 days. Concomitant therapy utilized rabeprazole, amoxicillin, clarithromycin, and metronidazole for 14 days.

These recommendations are appropriate for western developed countries that have ample information on *H. pylori* drug resistance, and where use of the relevant antibiotics is well regulated and documented. In sub-Saharan African, antibiotics use is not stringently regulated partly because of the many cases of bacterial infections. In a recent review, Tadasse and colleagues noted the lack of recent antimicrobial resistance data in many Sub-Saharan African countries. Data from few studies indicated high levels of resistance to antimicrobial agents[87]. Specific *H. pylori* drug resistance data are also not widely available for many Sub-Saharan African countries. The few available data show alarming high rates of *H. pylori* resistance to recommended antibiotics[13, 77, 88]. In a systematic review of reports from Africa, Jaka and colleagues reported 29.2 % resistance to clarithromycin, 75.8 % resistance to metronidazole, and 72.6 % resistance to amoxicillin[88].

Table 1. Summary of Current Consensus Statements on H. pylori Treatment

1	Prior antibiotic exposure should be determined before initiating *H pylori* treatment
2.	Choice of first-line antibiotic therapy should consider regional *H pylori* drug resistance pattern and eradication rates
3.	In regions with low resistance to clarithromycin (i.e. < 15 %), first-line therapeutic regimen (triple therapy) that includes clarithromycin may be effective
4.	Bismuth based quadruple therapy is highly recommended in areas with high clarithromycin resistance (i.e. > 15 %)
5.	Triple, quadruple, sequential, or concomitant therapy should extend to 14 days for optimal efficacy

CONCLUSION AND RECOMMENDATIONS

Sub-Saharan Africa lacks reliable data on the regional and intra-country prevalence of *H. pylori* infections. The association between *H. pylori* positivity and disease is not fully established in the region. There is also no current report on the appraisal of the efficacy of the triple and quadruple therapeutic strategies adopted by many countries. Information on drug resistance is scanty. The few available reports suggest a high rate of drug resistance. For these reasons, recommending a evidence-based therapeutic strategies is difficult.

The way forward for Africa is to recognize the clinical importance of this neglected pathogen in the region. More studies are needed to provide national and regional epidemiological data including data on drug resistance and disease association with *H pylori* infection in Sub-Saharan Africa. Regional diagnostic laboratories should be established to test *H pylori* susceptibility. A Pan-African conference on *Helicobacter pylori* could provide opportunity to brain-storm on *H pylori* pathogenicity, prevalence and drug resistance in Africa.

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