

# The *Helicobacter pylori* Eradication Rate in a High Prevalence Area (West Africa): Three Triple Therapy Comparative Study

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## Abstract

In Western countries, the current trend is to use sequential quadruple therapy or bismuth-based instead of triple therapy for the eradication of *Helicobacter pylori* (*H. pylori*). In sub-Saharan Africa, high prevalence area of the *H. pylori* infection, the effectiveness of these triple therapies widely used in routine has been little evaluated. The purpose of this study was to evaluate and compare the effectiveness of three patterns of first-line triple therapy based on combining a proton pump inhibitors (PPI), and 3 types of antibiotics: omeprazole (O), amoxicillin (A), clarythromycin (C) and metronidazole (M). Patients and Methods: This is a randomized clinical trial opened on 3 parallel arms: OAM (group 1 or G1), OAC (group 2 or G2) or OCM (group 3 or G3). The primary endpoint was *H. pylori* eradication rate after seven days triple therapy. *H. pylori* diagnosis infection was based on bacterium detection on the histological examination of the gastric biopsies. Histological control was performed 4 weeks after the end of treatment to assess *H. pylori* eradication rate. Results: The average age of our 153 patients included in the study (86 men) was  $44.33 \pm 11.72$  years. The main reason of the endoscopy was the dyspeptic syndrome (75.16%). The gastroscopy was normal in 28.76%. A Gastric or duodenal peptic ulcer was found in 17% of cases and gastropathy in 45.75%. Histologically, the GC was active in 90.9% of cases, follicular in 35.3% of cases, atrophic in 22.5% of cases and was associated with intestinal metaplasia (IM) in 5.2% of cases. Patients of these three groups (n = 64 for G1, n = 56 for G2 and n = 33 for G3) were comparable for age, gender, endoscopy indications, alcohol consumption history or smoking, and

**anti-inflammatory drugs taking. Approximately 23% of patients experienced adverse reactions. The overall *H. pylori* eradication rate was 22.3%. There was no significant difference *H. pylori* eradication rate depending on the treatment used (28.1%, 21.4% and 15.1% for G1, G2 and G3,  $p = 0.34$ ). Conclusion: The *H. pylori* eradication rate was poor regardless of the triple therapy used. It is desirable in the absence of bacteriological data on the primary and secondary resistance levels to optimize the eradication rate advocating the use of quadruple therapy at outset in first-line.**

## Keywords

*Helicobacter pylori*, Triple Therapy, Eradication, West Africa

## 1. Introduction

The *Helicobacter pylori* (*H. pylori*) infection is a public health problem not insignificant [1], which affects 20% - 50% of the population in industrialized nations and more than 80% in less developed countries [2] [3]. This bacterium is associated with many gastric or duodenal pathologies and extra-digestive [2]-[4]. In high incidence of gastric carcinoma areas, the *H. pylori* eradication is recommended to prevent the development of this disease [5]-[7].

The European treatment guidelines revised in 2005 [4] and amended again after the “Maastricht IV” meeting of November 2010 are almost gone because of the need to adapt to the resistances’ appearance more and more to the antibiotics of classic triple therapy. In Western countries, the current trend is to use sequential quadruple therapy or bismuth-based instead of triple therapy for the *H. pylori* eradication due to a decline in efficiency related to resistance problems for antibiotics [8] [9].

In sub-Saharan Africa, high prevalence area of the *H. pylori* infection, the effectiveness of these triple therapies widely used in routine has been little evaluated [10]. This widespread use of triple therapies could be explained by the low level of knowledge of general practitioners and the high cost of quadruple therapy.

The purpose of this study was to evaluate and compare the effectiveness of three patterns of first-line triple therapy based on combining a proton pump inhibitors (PPI): omeprazole (O) and 3 types of antibiotics: amoxicillin (A), clarithromycin (C) and metronidazole (M).

## 2. Patients and Methods

### 2.1. Study Oversight

Our study was conducted in the centre hospitalier et universitaire de Yopougon’s endoscopy unit from June 2010 through November 2011. This was a prospective, comparative study of 3 combinations of classic triple therapy for *H. pylori* eradication. During the period of the study, all patients that had to undergo a gastroscopy and had no indication against the realization of gastric biopsies were routinely included.

### 2.2. Exclusion Criterea

Pregnant women/or nursing mothers, patients with liver cirrhosis, renal failure, patients with a history of gastrointestinal surgery, gastroesophageal reflux disease, and those who had taken proton pump inhibitor, bismuth salts, H2 blockers and/or antibiotic treatment in the previous 2 months were excluded from the study.

### 2.3. Study Conduct

For each patient, we routinely practiced five gastric biopsies: two biopsy specimens (one each from the antrum and corpus) and one to angular stomach. Biopsy specimens were fixed in formalin at 10% and sent to Cocody (Abidjan) teaching hospital’s anatomy pathology laboratory. The histological assessment of *H. pylori* status was performed using a further four biopsy (stained with Giemsa), for histological examination to characterize chronic gastritis thanks to hematein eosin staining according to the Sydney system.

We included patients whose gastric biopsies were positive for *H. pylori* histology. To each patient it has been assigned by drawing lots one of three protocols of triple therapy for 7 days: G1 (n = 64): Omeprazole 20 mg +

Amoxicillin 1 g + Metronidazole 500 mg (OAM); G2 (n = 56): Omeprazole 20 mg + Amoxicillin 1 g + clarithromycin 500 mg (OAC); G3 (n = 33): Omeprazole 20 mg + clarithromycin 500 mg + metronidazole 500 mg (CMO). During the seven days, the capsules of Omeprazole, Amoxicillin, clarithromycin and metronidazole were taken twice daily (morning and evening before meals). Four weeks after the end of treatment, the effectiveness of each triple therapy was evaluated by performing a gastroscopy with five new gastric biopsies for histological analysis in search of a negativity or persistence of *Helicobacter pylori* infection in the same laboratory and using the same techniques mentioned above.

## 2.4. Studied Variables

The parameters studied were the age, the gender, the lifestyle (alcohol, tobacco), the reason for gastroscopy, the endoscopic and histological parameters, and the medication side effects.

All these data were collected on individual survey forms, entered and processed by Excel.

## 2.5. Ethics

Before the study began, the patients signed an informed consent form which included, age, gender, chief complaint, drug history and past medical history.

## 2.6. Statistical Analysis

Statistical analysis of the factors studied was made by a correct Chi<sup>2</sup> Pearson test to compare the different groups in terms of the general data, the eradication rate and side effects with a significance coefficient  $p < 0.05$ . Comparing the quantitative variables (average and median) was made by an analysis of variance (Anova).

## 3. Results

Over the period of our study we recruited 153 patients (86 men) with an average of  $44.33 \pm 11.72$  years. All patients included were positive to *H. pylori*. The demographic and clinical characteristics of these patients are reported in **Table 1**. Fifty-four point twenty five percent (54.25%) patients complained of chronic epigastric pain. Five patients were taking NSAIDs before treatment (**Table 1**). The main reason for endoscopy was the dyspeptic syndrome (75.16%). Gastroscopy found a gastric or duodenal peptic ulcer in 17% of cases and could not find mucosal lesion in 28.76%. The most important histological aspect associated with *H. Pylori* infection was gastritis' activity (90.9%), while atrophy and intestinal metaplasia were found respectively in 22.9% and 5.23% cases (**Table 2**). Thirty-five of the 153 patients, 22.9% had side effects including 30 patients who had nausea (19.6%), three had vomit (1.96%), one felt faint (0.65%) and one had nausea and vomit the same time (0.65%). The overall eradication rate in our study was low in the order of 22.9%. In univariate analysis, we noted no significant difference in *H. pylori* eradication rate among the three groups which were respectively 28.1%, 21.4% and 15.1% for G1, G2 and G3 (**Table 3**).

## 4. Discussion

Ivory Coast like most African countries is regarded as an area of high prevalence of the *H. pylori* infection

**Table 1.** Demographic and clinical characteristics of the patients at baseline.

	G1 (n = 64)	G2 (n = 56)	G3 (n = 33)	p value
Mean age $\pm$ SD ( year)	45 $\pm$ 10.63	44 $\pm$ 13.3	42.9 $\pm$ 11.60	0.56
Median age ( years)	45.5 (36.5 - 52)	44 (36.5 - 52)	43 (37 - 49)	
Male	36 (60.9%)	29 (51.8%)	18 (54.6%)	0.59
Alcohol consumption	1 (1.56%)	00 (0%)	00 (0%)	0.50
Tobacco consumption	0	0	0	
NSAIDs* taking	2 (3.1%)	3 (3.6%)	1 (3%)	0.98

NSAIDs\*: non-steroidal anti-inflammatory drug-related stomach.

**Table 2.** Histology results of patients included in the study.

Histology results	Frequency (%)
Chronic gastritis	153 (100%)
Active gastritis	149 (90.9%)
Follicular gastritis	54 (35.3%)
Atrophic gastritis	35 (22.9%)
Intestinal metaplasia	8 (5.2%)

**Table 3.** *H. pylori* eradication rate according treatment.

Treatment	Frequency (%)	p
OAM	18/64 (22.1%)	0.336
OAC	12/56 (21.6%)	
OCM	5/33 (15.2%)	

omeprazole (O), amoxicillin (A), clarithromycin (C), metronidazole (M).

where it affects over 80% of the population [11]-[14]. The role of the bacteria in the dyspeptic syndrome, peptic ulcers, and precancerous lesions of the stomach has been established [15]. Indications for research and treatment of *H. pylori* infection are the subject of an international consensus that has been taken up in various expert conferences, European or [4] [16], North American [6], Asian [7].

In many studies, the breath test with urea labeled with carbon-13 is still the most used examination for checking the efficiency of *H. pylori* eradicating treatments as noninvasive with excellent sensitivity and available in Western countries and Asia [15] [17]-[19].

In Ivory Coast, histological examination is the most used method for the *H. pylori* detection and the only way to control the eradication of bacteria because breath test is not available.

The 7-day triple therapy from PPI, clarithromycin and amoxicillin or metronidazole is the first-line eradication treatment of the *H. pylori* still prescribed by most general practitioners as European Consensus' recommendations [4] [20] [21] in Côte d'Ivoire.

This treatment's effectiveness was established in 1996, with an eradication rate of over 80% by intention-to-treat (ITT) [22]. Clinical trials that have been accumulated over the last decade show throughout the world a decrease of the effectiveness of this triple combination therapy with eradication rates below 70% [23]-[26] so that the current trend in the developed countries is the sequential therapy or bismuth-based quadruple therapy as first-line [15].

No published study has been made to our knowledge to assess and compare different classic triple therapy eradication of *H. pylori* in sub-Saharan Africa. We conducted this study in order to evaluate *H. pylori* eradication rate in Côte d'Ivoire by three triple therapy. We included in our study 153 patients divided into three groups according to the possible combinations of standard triple therapy (G1 = OAM, G2 = OAC and G3 = CMO). All patients were comparable with respect to gender, age, alcohol intake, tobacco or NSAIDs, as well as gastroscopy pattern.

We consider that both sexes are equally affected by the *H. pylori* infection [27], but some studies have noted a male predominance [13] [28] as in our studied sample with a rate of 56.21%. Unlike developed countries, *H. pylori* infection predominates with young adults in developing countries [11] [13] [19]. This is verified in our study with an average age of subjects infected with *H. pylori* which was 44.3 years. No case of normal gastric mucosa was found in our study. All had chronic gastritis confirming the *H. pylori* pathogenesis in its occurrence [29]. Precancerous lesions such as atrophy and intestinal metaplasia were found in respective proportions of 22.9% and 5.2%. These data are comparable with those found by other authors in the Ivory Coast [11] [30]. Despite these relatively low proportions of these precancerous lesions, the *H. pylori* infection treatment is still required.

Our results show that seven days of classic triple therapy used enable to obtain global eradication rates below 25% (22.9%). Although it is described a progressively high failure rate with standard triple therapy, our results

show very high failure rate (over 75%) in contrast to more work done in the West and Asia that show rates increasing gradually to reach 40% failure since the 2000s [8] [17] [25]. In these studies predictors of failure were mainly of antibiotic resistance strains especially to clarithromycin and poor medical compliance; other factors seem to have no significant effect (alcohol, tobacco, food) [31] [32].

In our study, we certainly did not assess treatment adherence, but all patients took all their *H. pylori* eradication treatment, despite the gastrointestinal occurrence side effects about 30% of patients. Therefore, we cannot attribute this therapeutic failure to poor compliance therapy neither in the tobacco nor the alcoholic because no patient took snuff and only one patient was alcohol consumer. Antibiotic resistance is the main factor contributing to the failure of PPI-based triple therapies for the *H. pylori* eradication adequately. Amoxicillin currently seems untouched by the resistance problem. Indeed, the highest rate of resistance is now described below 1% [8]. However, various studies show a high rate of strains resistant to clarithromycin, which rose from 15% to over 20% [8] [33]-[35].

This rate is 13% in African countries where the molecule has been tested [36]. The metronidazole resistance would cover up to 59% of strains [33] in the West. In Africa, this *H. Pylori* eradication rate is variable. In Senegal, it is estimated at 90% in Seck's study [37]. While this rate is 55% in Nigeria [36].

The prevalence of resistance in 2009 in France evaluated on 530 strains showed that 13% were resistant to both clarithromycin and metronidazole [33]. The primary resistance appearance to clarithromycin is the major cause of the inefficiency of clarithromycin-based triple therapy [38]. This resistance is associated to different mutations in the V domain of the 23S ribosomal RNA gene [39]. The clinical impact of resistance to metronidazole is lower [32].

The triple therapy having lost its effectiveness in the past decade, several quadruple therapies combining a PPI with amoxicillin, clarithromycin and a nitro-imidazole (metronidazole or tinidazole) or bismuth have been studied. A meta-analysis incorporating 10 controlled trials in 3006 patients shows that the sequential therapy permitted to obtain a significantly higher eradication rates (91.0% eradication; 95% CI: 89.6 to 92.1) than the triple therapy containing clarithromycin or metronidazole (75.7% eradication; 95% CI: 73.6 to 77.7) [40].

This result was associated with better efficacy of sequential therapy on strains resistant to clarithromycin. In the same study, with 45 patients with resistant strain, *H. pylori* eradication rate was 83.3% (95% CI: 60.8 to 94.2) with the sequential therapy and 25.9% (95% CI: 13.2 to 44.7) with triple therapy. The compliance and safety of the sequential therapy seemed as good as that of the clarithromycin triple therapy based. Finally, concurrent and sequential quadruple therapy tolerances seemed equivalent [41].

Furthermore, an European multi-centre randomized study showed more eradication rates with bismuth -based quadruple therapy than with clarithromycin-based triple therapy: 93% (95% CI: 89% - 97%) in per-protocole (PP) and 80% (95% CI: 74% - 85%) ITT versus 70% (CI 72% - 77%) in PP and 55% (CI 49% - 62%) in ITT ( $p < 0.0001$ ) [42].

Two other studies previously had found comparable eradication rates [43]. The frequency of adverse effects of bismuth-based quadruple therapy is comparable to those of the clarithromycin-based triple therapy [44]. In countries where it is permitted, the bismuth-based quadruple therapy is an alternative to sequential processing and can be used with patients allergic to beta-lactams or macrolides receiving whatever the indication.

The study limitations are small number of patients and absence compliance therapy evaluation.

## 5. Conclusion

Seven days of anti *H. pylori* triple therapy in a high prevalence context with poor overall results. It is desirable in the absence of bacteriological data on the primary and secondary resistance levels to optimize the eradication rate advocating the immediately use of quadruple therapy in first intention.

## Conflict of Interest

Authors declare having not got conflict of interest.

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