

Original Research Article

Efficacy of 4 quadruple therapy to eradicate *Helicobacter pylori* in the real-life

DoffouAdjéka Stanislas^{1,3,4,6}, Assi Constant^{2*}, Illa Hamidine^{1,5}, Bangoura Aboubacar Demba^{1,6,7,8}, Kouamé Dimitri¹, Allah-Kouadio Emile², Nigue Luc⁹, Anzouan-Kissi Henriette^{1,3}, Mahassadi Alassan Kouamé¹, Yao Bathaix Fulgence¹, Attia Koffi Alain^{1,3}, Lohouès-Kouacou Marie-Jeanne²

¹Department of Gastroenterology of Yopougon teaching hospital

²Department of Gastroenterology of Cocody teaching hospital

³Danga Medical Clinic, Cocody, Abidjan, Côte d'Ivoire

⁴Rosette Medical Clinic, Treichville, Abidjan, Côte d'Ivoire

⁵Big Center Medical Clinic, Yopougon, Abidjan, Côte

⁶Officials Medical Service, Plateau, Abidjan, Côte d'Ivoire

⁷Oliviers Medical Center, Yopougon, Abidjan, Côte d'Ivoire

⁸Mamie Adjoua Medical Clinic, Yopougon, Abidjan, Côte d'Ivoire

⁹Departement of biostatistic, university of Cocody

Received: 10-05-2021 / Revised: 01-06-2021 / Accepted: 25-07-2021

Abstract

Background: The effectiveness of rate of eradication *Helicobacter pylori* is unknown in Côte d'Ivoire in daily practice. **Objectives:** The aim of our study was to assess the effectiveness of 4 quadruple therapies. **Materials and Methods:** This was a retrospective multi-center study carried out in Abidjan. The medical records of naive patients over 18 years old treated with quadruple therapy [sequential (Qs), concomitant 10 (Qc10) or 14 days (Qc14) or bismuth based therapy (Qb)] confirmed histologically on gastric biopsies were included. All had a histological check for the eradication of *H. pylori* at least 4 weeks after the end of treatment. The quadruple therapy eradication rate has been determined. **Results:** One hundred and seventy files were included. The overall eradication rate was 60.6% [53.3% - 67.9% 95% CI]. It was 55.6% for Qs (30/54, [42.3% - 68.9% 95% CI]), 80% for Qc10 (8/10, [55.2% - 100% 95% CI]), 58.3% for Qc14 (49/84, [47.756%, 68.844% 95% CI]) and 72.7% for Qb (16/22, [54.084%, 91.316% 95% CI]). The patients of the 4 protocols were comparable for age ($p = 0.054$); gender ($p = 0.157$); reason ($p = 0.173$) and endoscopy result ($p = 0.244$); intensity of antral ($p = 0.542$) and fundic ($p = 0.744$) *H. pylori* infection in histology; frequency of side effects ($p = 0.131$) and adherence to therapy ($p = 0.564$). **Conclusions:** The eradication rate of *H. pylori* in daily practice was not optimal regardless of the quadruple therapy regimen used. A study of the resistance of *H. pylori* to different antibiotics is necessary.

Key word: *Helicobacter pylori*- quadruple therapy -eradication- endemic country - real life.

This is an Open Access article that uses a fund-ing model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Helicobacter pylori (*H. pylori*) is a spiral bacteria discovered in 1982 [1]. The bacteria infects 50% of the world's population, which can reach 80% in Africa when the infection is acquired during childhood [2]. *H. pylori* is involved in the genesis of peptic ulcers, gastric cancer and MALT lymphoma [3,4]. It is a carcinogenic bacterium [5]. Eradicating *H. pylori* infection reduces the recurrence of peptic ulcers and the risk of gastric cancer [6]. Many therapeutic regimens are offered; their effectiveness varies according to the regions of the world, depending on the resistance of *H. pylori* to antibiotics [7]. Currently, given the drop in the eradication rate of *H. pylori*, the recommended protocols for first-line therapy are bismuth and non-bismuth (quadruple and concomitant) quadruple therapy of 10 or 14 days [8]. The main antibiotics in these four therapies are clarithromycin, amoxicillin, metronidazole, tetracycline and bismuth salts [7]. In Cote d'Ivoire, there are no published studies on the eradication rate of *H. pylori*. The objective of our study was to assess the rate of eradication of *H. pylori* according to the quadruple therapy schema used.

*Correspondence

Dr. Assi Constant

Department of Gastroenterology of Cocody teaching hospital

E-mail: assiconstant@yahoo.fr

Materials and methods

This was a retrospective (January 2016 to December 2018) multi-center study (8 public and private hospitals) carried out in Abidjan. The medical records of patients of both sexes over the age of 18 who were naive of any treatment for the eradication of *H. pylori* followed by a gastroenterology consultation for chronic gastritis discovered during the histology of gastric biopsies taken during a gastroscopy were included. The medical records of patients who have not been treated with one of the 4 quadruple therapy protocols, or who have not completed treatment or who have not had a histological check at least 4 weeks after the end of treatment during gastroscopy with gastric samples and unusable records were excluded from the study. The four *H. pylori* eradication protocols studied were: sequential quadruple therapy or Qs (double dose PPI and amoxicillin 1 g twice a day for 5 days, then PPI and metronidazole 500 mg combined with clarithromycin 500 mg twice a day for 5 days), concomitant quadruple therapy (PPI combined with clarithromycin 500 mg, Metronidazole 500 mg and amoxicillin 1 g twice a day) for 10 days (Qc10) or 14 days (Qv14) and bismuth quadruple therapy for 10 days (Qb). The data was collected from the files of patients followed up for consultation in the various sites using a standardized sheet. Age, sex, history (Alcohol, tobacco, taking an antibiotic or gastric antisecretory in the month preceding the start of the quadruple therapy), the eradication protocol as well as the adherence and side effects of the quadruple therapy prescribed by the practitioner were collected there.

From the initial gastroscopy report and the eradication control report, the reason and the result of the examination were noted. The endoscopic anomalies were grouped into 3 lesions: gastric ulcer, duodenal ulcer and gastritis. From the histology result of gastric biopsies during the initial and control gastroscopy, the density of *H pylori* according to the Sydney classification (0 = absent; 1 = minimal; 2 = moderate; 3 = severe) was also noted. Qualitative variables were presented as a percentage with their 95% confidence interval, quantitative variables as median and average with their standard deviation. The overall eradication rate defined by the proportion of patients included who had had an eradication of *H pylori* under histological control over all the patients treated, as well as its 95% confidence interval. The comparability of the 4 s / groups according to the prescribed quadruple therapy was analyzed according to clinical, endoscopic and histological parameters. For each quadruple therapy protocol, the rate of *H pylori* eradication (proportion of patients who had an eradication of *H pylori* under histological control over all patients treated with quadruple therapy) as well as its confidence interval at 95 % had been determined. The effect of the quadruple therapy considered on the histological clearance of *H pylori* was measured by comparing the evolution of the histological rating of *H pylori* according to the Sydney system before and after treatment. The mean rating of the intensity of *H pylori* gastric infection after treatment was compared to that before treatment in paired series using the Wilcoxon test. The distribution of ratings

was presented on average and in standard deviation (SD). The alpha significance threshold was set at 5%. The analysis of the results was carried out by IBM SPSS Statistics SPSS 26.0 software (IBM Corp. Chicago, USA). The study was consistent with the Helsinki Declaration. The study had the agreement of the "comité national d'éthique des sciences de la vie et de la santé" of Côte d'Ivoire.

Results

During the study period, 700 files of patients who had a histology of biopsies after gastroscopy concluding that *H pylori* was present were collected. Five hundred and thirty files were excluded for lack of histological control of the eradication or for interruption of the prescribed treatment or for unusable file. A total of 170 medical records were analyzed in the study. Among them, 103 had an eradication of *H pylori*, ie an overall eradication rate of *H pylori* of 60.6% [53.3% - 67.9%]. Quadruple therapy, 10-day concomitant, 14-day concomitant and bismuth based therapy were prescribed respectively in 31.8% (n = 54); 5.9% (n = 10); 49.4% (n = 84) and 12.9% (n = 22) of the cases. The patients of these 4 protocols were comparable for age (p = 0.054), sex (p = 0.157), smoking (p = 0.654), alcoholism (p = 0.625), taking the antibiotic before quadruple therapy (p = 0.898), the antral (p = 0.542) and fundic (p = 0.710) distribution of *H pylori*. The distribution of quadruple therapy eradication treatments was significantly different according to the inclusion centers (p = 0.001). Table 1 compares the characteristics of the patients of the 4 quadruple therapy prescribed

Table 1: Characteristics of the 4 groups of quadruple therapy for eradicating *H pylori* prescribed.

Variables	Qs [†] n = 54		Qc10 [‡] n = 10		Qc14 [‡] n =84		Qb [§] n =22		P
Recruitment center									<0.0001
0	17	31.5%	2	20%	33	39.3%	3	13.6%	
1	18	33.3%	3	30%	17	20.2%	12	54.5%	
2	0	0	0	0	3	3.6%	0	0	
3	6	11.1%	0	0	3	3.6%	0	0	
4	5	9.3%	4	40%	8	9.5%	0	0	
5	4	7.4%	1	10%	6	7.1%	2	9.1%	
6	3	5.6%	0	0	11	13.1%	0	0	
7	1	1.9%	0	0	3	3.6%	5	22.7%	
Male %	(32/54) 59.3%		(6/10) 60%		(34/84) 40.5%		(11/22) 50%		0.157
Mean age	46.3±10.3		48.2±15.1		49.8±12.2		54.7±12.2		0.054
Medical History									
Antibiotic	1	1.9%	0	0	1	1.2%	0	0	0.898
Alcohol	14	25.9%	1	10%	21	25%	7	31.8%	0.625
Tobacco	2	3.7%	0	0%	1	1.2%	1	4.5%	0.654
Indication of gastroscopy									0.173
Epigastralgia	47	87%	7	70%	70	83.3%	16	72.7%	
Anaemia	1	1.9%	0	0	1	1.2%	0	0	
Halitosis	2	3.7%	0	0	7	8.3%	1	4.5%	
Vomiting	0	0	1	10%	2	2.4%	0	0	
Other	4	7.4%	2	20%	4	4.8%	5	22.7%	
Antral <i>H pylori</i>									0.542
0	1	1.9%	0	0%	3	3.6%	0	0	
1	17	31.5%	2	20%	22	26.2%	11	50%	
2	19	35.2%	5	50%	34	40.5%	4	18.2%	
3	17	31.5%	3	30%	25	29.8%	7	31.8%	
Fundic <i>H pylori</i>									0.710
0	7	13%	1	10%	7	8.3%	1	4.5%	
1	17	31.5%	2	20%	24	28.6%	11	50%	
2	15	27.8%	4	40%	31	36.9%	5	22.7%	
3	15	27.8%	3	30%	22	26.2%	5	22.7%	
Gastroscopy results									0.244
duodenal ulcer	6	11.1%	2	20%	4	4.8%	1	4.5%	
Gastric ulcer	0	0	1	10%	2	2.4%	0	0	
No lesion	13	24.1%	0	0	19	22.6%	7	31.8%	
Gastritis	35	64.8%	7	70%	59	70.2%	14	63.6%	

†sequential quadruple therapy.‡concomitant quadruple therapy.§Bismuth quadruple therapy

There was no significant difference between the eradication rates of *H pylori* from the 4 four-drug regimens ($p = 0.297$). Table 2 shows the eradication rates of *H pylori*, the side effects and the compliance with the 4 quadruple therapy eradication therapies.

Table 2: H pylori eradication rate compliance and side effects of the 4 treatments prescribed.

Variable	Qs [†]		Qc10 [‡]		Qc14 [‡]		Qb [§]		P
Eradication rate	30/54 55.6% [42.3%- 68.9%]		8/10 80% [55.2%-100%]		49/84 58.3% [47.8%- 68.8%]		16/22 72.7% [54.1%-91.3%]		0.297
Observance									0.564
Good	52	96.3%	9	90%	81	96.4%	22	100%	
Bad	2	3.7%	1	10%	3	3.6%	0	0	
Side effects									0.131
No	51	94.4%	9	90%	77	91.7%	17	77.3%	
Yes	3	5.6%	1	10%	7	8.3%	5	22.7%	
Type of side effect									
Diarrhea	1	1.9%	0	0	1	1.2%	1	4.5%	
Abdominal pain	4	7.4%	1	10%	3	3.6%	1	4.5%	
Pruritus	1	1.9%	0	0	0	0	0	0	
Headache	2	3.7%	1	10%	1	1.2%	0	0	
Vertigo	0	0	0	0	1	1.2%	0	0	
hypersialorrhea	0	0	0	0	3	3.6%	0	0	
Malaise	2	3.7%	1	10%	3	3.6%	0	0	
Anorexia	0	0	0	0	5	6%	0	0	

† Sequential quadruple therapy. ‡ Concomitant quadruple therapy; § Bismuth quadruple therapy

There was a significant decrease in the intensity of *H pylori* infection at the gastric histology before and after treatment for sequential quadruple therapy, concomitant quadruple therapy for 10 days and 14 days, and for bismuth quadruple therapy for 10 days (Table 3).

Table 3: Evolution of the intensity of gastric infection with H pylori in histology according to the prescribed quadruple therapy

Protocole		Median (IQR†)	Mean (SD‡)	P
Sequential quadruple therapy	Before	2 (1-3)	2.00 (0.80)	<0.0001
	After	0 (0-2)	0.80 (1.02)	
Concomitant Quadruple Therapy for 10 days	Before	2 (2-3)	2.10 (0.74)	0.0046
	After	0 (0-0)	0.20 (0.42)	
Concomitant quadruple therapy for 14 days	Before	2 (1-3)	2.02 (0.79)	<0.0001
	After	0 (0-1)	0.63 (0.90)	
Bismuth quadruple therapy	Before	1.5 (1-3)	1.82 (0.91)	0.0001
	After	0 (0-1)	0.45 (0.91)	

† Interquartile ratio; ‡ standard deviation

Discussion

The overall eradication rate of *H pylori*, assessed from medical record data in our study, was 60.6%. The most commonly used regimen in the study centers was 14-day concurrent quadruple therapy with 49.4% of medical prescriptions ($n = 84$). This schema is one of the protocols recommended in first intention [7]. None of the 4 studied schemas allowed an eradication rate of more than 80% in daily practice. A rate below 80% of an eradication protocol is considered insufficient for first-line use in clinical practice [7]. According to Graham et al, the goal of first-line treatment for the eradication of *H pylori* is to achieve an eradication rate of 90% [9]. Currently, the eradication of *H pylori* remains an unsolved problem. Indeed, no treatment regimen is capable of curing the infection in all treated patients, and in many the infection persists despite the administration of several consecutive standard therapies [10]. Results from clinical studies in Africa and elsewhere on different eradication protocols yielded widely varying results, although 14-day and bismuth quadruple therapy had the best eradication rates (Table 4 [14]). In the only black African study published on 14-day quadruple therapy, the eradication rate of *H pylori* was higher than in our work (88%) [12]. In

our study, one of the inclusion criteria was to have respected the duration and the dosage of the prescribed drugs. Adherence to treatment was good in 164 patients (96.5%) despite the occurrence of side effects in 32 patients (18.8%). These side effects have been reported in other studies [11, 12]. To our knowledge, the level of resistance of *H pylori* to antibiotics is unknown in Côte d'Ivoire; it has also been little studied in Africa [13]. However, our work has shown that all 4 first-line regimens resulted in a significant reduction in the intensity of *H pylori* gastric infection during the control histology. This finding could suggest that a longer duration of treatments would eradicate the bacteria. The design of our study showed that in real life, given the high number of unsuccessful files (530/700), that several patients abandoned their treatments before its end and that the eradication controls in post therapy were not done in the majority of cases.

Conclusion

The eradication rate of *H pylori* in daily practice was insufficient regardless of the regimen of the first-line therapy prescribed in Abidjan. A study of the bacteria resistance to antibiotics is necessary.

Author contribution

Doffou Adjéka Stanislas, Assi Constant, AttiaKoffi Alain, Lohouès-Kouacoumarie-Jeanne contributed to the conception or design of the work;

Illa Hamidine, Bangoura Aboubacar Demba, KouaméDimitri, Kouadio Emile, Nigue Luc, Anzouan-KissiHenriette, Mahassadi Alassan Kouamé, Yao Bathaix Fulgence contributed to the acquisition of the result. Doffou Adjéka Stanislas, Assi Constant, Nigue Luc, Attia Koffi Alain and Lohouès-Kouacou Marie-Jeanne analysed the result. Doffou Adjéka Stanislas, Assi Constant, AttiaKoffi Alain, Lohouès-Kouacoumarie-Jeanne contributed to the interpretation of data for the work.

Doffou Adjéka Stanislas, Assi Constant, IllaHamidine, Bangoura Aboubacar Demba, KouaméDimitri, Kouadio Emile, Nigue Luc, Anzouan-Kissi Henriette, Mahassadi Alassan Kouamé, Yao Bathaix Fulgence, Attia Koffi Alain, Lohouès-Kouacoumarie-Jeanne had drafting the work or revising it critically for important intellectual content.

Doffou Adjéka Stanislas, Assi Constant, IllaHamidine, Bangoura Aboubacar Demba, Kouamé Dimitri, Kouadio Emile, Nigue Luc, Anzouan-Kissi Henriette, MahassadiAlassanKouamé, Yao Bathaix Fulgence, AttiaKoffi Alain, Lohouès-Kouacoumarie-Jeanne approved the final version to be published.

References

1. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach patients with gastritis and peptic ulceration. *Lancet* 1984;1:1311-15.
2. Smith SI, Pellicano R. *Helicobacter pylori* infection in Africa: 2018 literature update. *Minerva Gastroenterol Dietol* 2018;64:222-234
3. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process. First american cancer society award lecture on cancer epidemiology and prevention. *Cancer Res* 1992;52: 6735-40.
4. Kenneth MC. *Helicobacter pylori* infection; *New England Journal of Medicine* 2010; 362:1597-1604.
5. Peek RM, Blaser MJ. *Helicobacter pylori* and gastro-intestinal tract adenocarcinomas. *Nat Rev Cancer* 2002;2:28-37.
6. Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. *Gut*. 2020 Mar 23. pii: gutjnl-2020-320839.
7. Malfertheiner P, Megraud F, O'Morain CA, Gisbert J P, Kuipers E J, Axon A T et al. Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. *Gut* 2017;66:6-30.
8. Zhou Y, YeZ , Wang Y, Zhang Y, Tang Z, Yanet W et al. Comparison of four different regimens against *Helicobacter pylori* as a first-line treatment: A prospective, cross-sectional, comparative, open trial in Chinese children. *Helicobacter* 2020;25:e12679.
9. Graham DY, Dore MP, Lu H. Understanding treatment guidelines with bismuth and non-bismuth quadruple *Helicobacter pylori* eradication therapies. *Expert Rev Anti Infect Ther* 2018;16:679-687.
10. Ierardi E, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change *Helicobacter pylori* treatment: A matter of geography? *World J Gastroenterol*. 2013; 19:8168-80.
11. Ozturk O, Ulasoglu C, Ozdil K et al. Therapeutic success with bismuth-containing sequential and quadruple regimens in *Helicobacter pylori* eradication. *Arab J Gastroenterol* 2017; 18:62-67.
12. Kabakambira JD, Hategeka C, Ntiringanya C, Dusabejambo V, Ndoliet J et al. Efficacy of *Helicobacter pylori* eradication regimens in Rwanda: a randomized controlled trial. *BMC Gastroenterol*. 2018;18:134-9.
13. Smith S, Pellicano R. Infections with *Helicobacter pylori* and challenges encountered in Africa. *World J Gastroenterol* 2019;25:3183-3195.

Conflict of Interest: Nil

Source of support: Nil