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Assessing of the Therapeutic Efficacy of These 2 Treatment Regimens in the Management of *Helicobacter pylori* Infection at Kinshasa

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Abstract

Introduction: *Helicobacter pylori* (Hp) infection is a worldwide public health problem. Unfortunately, its management poses a problem because of resistance to antibiotics. However, there are codified treatment protocols covering sequential and concomitant quadritherapy with regard to first-line probabilistic treatment. The objective of this study was to assess the therapeutic efficacy of these 2 treatment regimens in the management of Hp infection at Kinshasa. **Methods:** This was a mixed study, with documentary, descriptive and interventional approaches, carried out between September 1, 2018 and April 30, 2020. **Results:** Sixty-four patients were collected, including 36 men against 28 women with a sex ratio of 1H:1F; the mean age was 54 ± 16.5 years. There was an over-representation of senior patients (n = 29); an intermediate number of adult patients (n = 22) and a lower number of young patients (n = 13). 34 and 30 were respectively treated according to the concomitant and sequential regimens. Concomitant quadruple therapy offered an eradication rate of 91.2% compared to 56.7% for sequential quadruple therapy; concomitant treatment, advancing age and absence of risky behavior more quickly predicted the occurrence of eradication success. **Conclusion:** The present study showed superiority of concomitant quadruple therapy over sequential quadruple therapy in first-line treatment. Alcohol with active smoking had a

negative influence, while concomitant quadruple therapy, advancement in age had a positive influence on the success of the eradication of Hp infection.

Keywords

Helicobacter pylori, Concomitant Quadruple Therapy, Sequential Quadruple Therapy, Eradication, Kinshasa

1. Introduction

Helicobacter pylori (Hp) is a gram-negative microaerophilic bacterium that infects the epithelial mucosa of the stomach [1]. It is a universally prevalent condition and is currently recognized as a public health problem, as prevalence of up to 90% has been reported in several regions of the world [2]. The areas with the highest prevalence are Africa, South America, China and India. This situation is explained by the poor socio-economic and hygienic conditions in these regions [2]. The modes of transmission of *H. pylori* remain unclear. However, given the differences in infection rates between developed and developing countries and between urban and rural areas, socioeconomic factors appear to contribute to the transmission of this infection. In most regions, the main mechanism of spread is interfamilial transmission [1] [3] [4] [5] [6] [7].

In 2015, approximately 4.4 billion people worldwide were estimated to be positive for Hp [4]. The highest prevalence of *H. pylori* was found in Africa (79.1%), Latin America and the Caribbean (63.4%), and Asia (54.7%), and the lowest prevalence in North America (37.1%) and Oceania (24.4%) [8]. However, the prevalence of *Helicobacter pylori* infection has decreased in recent decades due to improved sanitation, socio-economic development and better living conditions.

Unfortunately, the prevalence remains high in developing countries.

The high prevalence of Hp infection is compounded by the problem of its management [9] [10] [11]. Indeed, eradication of *Helicobacter pylori* infection has become more difficult over the last decade due to the increase in antimicrobial resistance, particularly to clarithromycin and levofloxacin [11] [12] [13]. In a recent study conducted in Kinshasa, disturbing rates of in vitro resistance were reported in the study population [14].

While in the Western world, studies of bacterial ecology have led to the establishment of well codified therapeutic regimens, these are lacking in developing countries, forcing them to align themselves with Western protocols [15]

The 2017 CAG guidelines describe first-line treatment strategies that include clarithromycin triple therapy, bismuth quadruple therapy, concurrent quadruple therapy, sequential quadruple therapy, hybrid therapy, levofloxacin triple therapy, and fluoroquinolone quadruple therapy [16].

Italian researchers have described eradication rates of more than 80% with sequential probabilistic quadruple therapy and close to 73% with Clarithromycin

resistance [17]. The efficacy of concurrent quadruple therapy has been demonstrated in several randomized trials and meta-analyses with eradication rates ranging from 85% to 94% [18].

The October 2015 European Consensus Conference or Maastricht V recommends abandoning sequential therapy in favor of concomitant and bismuth quadritherapy, with bismuth offering an eradication rate of over 90% [18] [19] [20].

In the DRC, the extent of Hp has been demonstrated through prevalence found in various studies conducted in the provincial city of Kinshasa [21] [22] [23] [24]. Unfortunately, there is no common protocol for the management of this infection. Some still use triple therapy as first line, others use quadruple therapy over ten days, and others use fourteen days, either sequentially or concurrently. This disparity offers a good number of resistances and does not increase the eradication rate of Hp infection. However, the study conducted in Kinshasa by Lamarque *et al.* [25] clearly showed the superiority of fourteen-day therapy over other therapeutic modalities, without distinguishing between concurrent and sequential four-day therapy. The unanswered question in this study was which of the four-therapy regimens, sequential or concurrent, provided a better eradication rate.

In fact, there is already a well-established first line management protocol in the West based on the recommendations of the Maastricht V consensus [17] [18] [19] [20]. It would be interesting to see how effective one or the other therapeutic regimen is in the Kinshasa population.

2. Methods

This was a mixed-methods study, involving literature (secondary analysis, retrospective), analytic, and interventional approaches. It included all 64 patients with *helicobacter pylori* infection followed from September 2018 to April 2020 total duration of 18 months. The study setting was the Cinquantenaire Hospital, Médical Diamant, Médical Candeur, Spécialisé de Kinshasa, Médical de Kinshasa, and Biomédical de Kinshasa.

All patients were dyspeptic with Hp infection after the rapid urease test, treated according to the concomitant and sequential therapeutic modalities (respectively 34 and 30) and submitted to the eradication control 4 weeks after treatment by detection of Hp antigen in the stool.

2.1. Data Collection

Data were collected using the OCIP mobile application (Aurore Foundation©, DRC, 2018) developed for the study by the *H. pylori* infection observatory of the Aurore Foundation, which is a nonprofit association that fights digestive cancers in the DRC.

2.2. Variables of Interest

The parameters of interest were age, sex, alcohol excess associated with active

smoking (yes or no), results of rapid urease test (positive or negative), treatment (concurrent or sequential quadritherapy), results of stool antigen test (positive or negative).

2.3. Operational Definitions

Some operational definitions were considered in this study.

H. pylori infection was having a positive rapid urease test.

An adult patient was considered to be between 40 and 50 years of age and a young patient was considered to be under 40 years of age.

The senior citizen was any patient at least 60 years old.

Senility was the fact of being over 40 years old.

For the endpoint, eradication was defined as a negative repeat stool test for *H. pylori* at least 4 weeks after the end of treatment.

2.4. Statistical Analysis

Statistical analyses included evaluation, validation, comparison, and inference of the data using SPSS version 25 software. File cleaning ensured quality control of univariate, bivariate, and multivariate statistical analyses.

For the univariate analyses, the categorical data (qualitative and nominal) were presented in the form of frequency (number = n) and proportions (percentages).

To do this, Pearson's Chi-square test was used to compare the percentages between two groups while Chi-square with trend was used to compare the percentages between > to 2 groups to highlight the biological gradient.

The quantitative or continuous variables were summarized as mean ± standard deviation according to their normal (symmetric) and abnormal distribution. Thus, Student's t-test and ANOVA compared the means of normally distributed variables between two groups, respectively.

For bivariate analyses, the simple coefficient "r" measured a possible association between two variables, categorical and quantitative.

For the multivariate analysis, the Cox regression model was used to determine the proportional hazard ratio with 95% confidence interval (CI) to determine the time from inclusion to eradication (survival time) as the dependent variable according to the incidence rate of eradication of Hp infection as a factor. Thus, Kaplan Meier survival curves were generated to identify the most important, independent and significant predictors according to the Log Rank test (comparison of survival time means).

Regarding statistical inferences, the following steps were rigorously followed:

- The null hypothesis H0 for suggesting no difference between two variables versus the alternative hypothesis H1 suggesting a statistically significant difference between two variables;
- Obtaining the value of probability $P < 0.05$ as a threshold of statistical significance.

3. Results

3.1. Predictors of Eradication Success

3.1.1. Gender

The impact of sex was neutral on the eradication of Hp infection:

77.8% (n = 28/36) success rate in men, similar (P = 0.561) to the 71.4% success rate in women (n = 20/28) (Table 1).

3.1.2. Age

There was a highly significant quadratic relationship (P = 0.002) in letter "J" between Hp eradication success and age advancement: the proportions of success being respectively highest at the extremes of age (senior-senior age and young age versus the nadir (hole) of Hp eradication success (Figure 1).

Table 1. Shows sociodemographic and clinical characteristic of the study population.

	Frequency	Percentage
Sex		
Men	36	56.3
Women	28	43.7
Risky behaviour		
Binges drinking and actives smoking	41	64
No risky behavior	23	36
Therapeutic modalities		
Sequential	30	46.9%
Concomitant	34	53.1
Eradication of Hp infection	Success	Failure
Male	77.8% (n = 28)	22.2% (n = 8)
Female	71.4% (n = 20)	28.6% (n = 8)

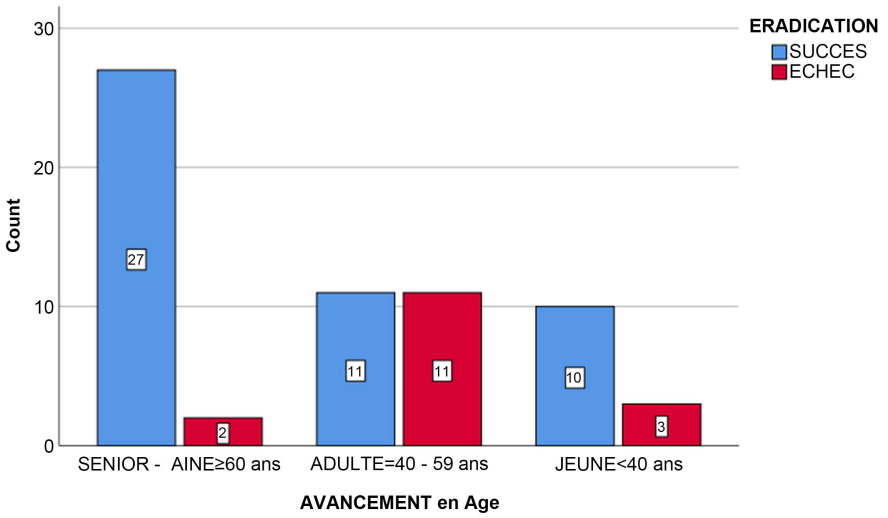

Figure 1. Success in eradicating Hp infection in relation to advancing age.

3.1.3. Risky Behaviour

Not surprisingly, successful eradication of Hp infection was more frequent in the absence of alcohol-active smoking (95.5%; n = 22/23) than in the presence of alcohol-active smoking (63, 4%; n = 26/41), with the statistical difference being highly significant (P = 0.004) (Figure 2).

3.1.4. Therapeutic Modalities

Successful eradication of Hp infection was more frequent in the concomitant type of therapy (91.2%; n = 31/34) than in the sequential type of therapy (56, 7%; n = 17/30), the statistical difference being highly significant (P < 0.001) (Figure 3).

3.2. Eradication Success Survival Function

3.2.1. Survival Function and Therapeutic Modalities

Considering survival function time as a dependent variable, concomitant treatment predicted the occurrence of eradication success faster (mean time = 11.3 ± 1.245;

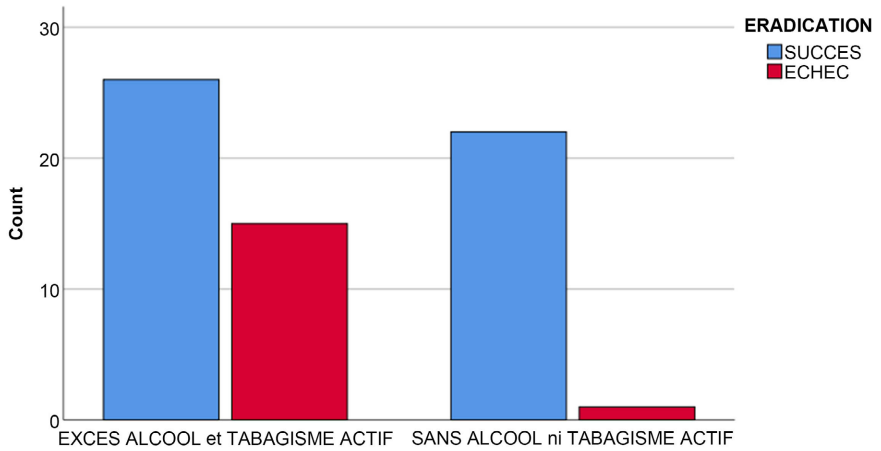

Figure 2. Eradication success versus risk behavior.

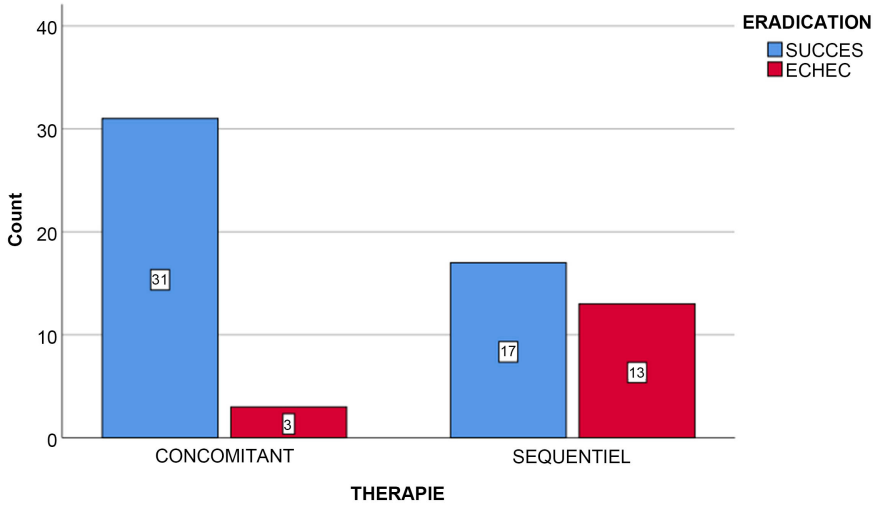

Figure 3. Successful eradication of Hp infection in relation to therapeutic modalities.

95% CI: 8.9 - 13.7 days) than did sequential treatment (mean time = 26.1 ± 0.956; 95% CI: 24.2 - 27.9 days), the statistical difference being highly significant (Log Rank (Mantel-cox) Chi-square = 29.530; degree of freedom = 1; P < 0.0001) according to Kaplan Meir curves (**Figure 4**).

3.2.2. Risky Behaviour

Considering the time of survival function as a dependent variable, the absence of risky behavior predicted the occurrence of eradication success faster (mean duration = 12.6 ± 1.646; 95% CI: 9.3 - 15.8 days) than did the risky behavior (mean duration = 21.4 ± 1.445; 95% CI: 18.6 - 24.2 days), the statistical difference being highly significant (Log Rank (Mantel-cox) Chi-square = 14.100; degree of freedom = 1; P < 0.0001) according to the Kaplan Meier curves (**Figure 5**)

3.2.3. Age

Considering the survival function time as a dependent variable, the mean durations were summarized around 17 days for senior-senior and young age versus the mean duration around 21 days in adults, the statistical difference being significant (Log Rank (Mantel-cox) Chi-square = 7.294; degree of freedom = 2; P < 0.026) according to Kaplan Meir curves (**Figure 6**).

4. Discussion

This chapter has commented on the most important results according to the objectives achieved and with regard to certain data in the literature. Indeed, this study examined the socio-demographic characteristics, risk behaviors, therapeutic modalities, and predictors of success in eradicating *Helicobacter pylori* infection in patients followed in different hospital institutions in Kinshasa and subjected to sequential quadruple therapy and concomitant quadruple therapy.

4.1. Hp Infection and Sociodemographic Characteristics

4.1.1. Gender

Although some authors [10] [26] [27] support a small contribution of sex differences in the prevalence of Hp infection, there is still controversy as to the predominance of one or the other sex on this prevalence. Indeed, for some data in the literature, the prevalence of *H. pylori* is equal in both sexes, which is in agreement with the prevalence of Hp(+) observed in the 2009 Janulaityte-Gunther study [28] and by other authors [27] [29]

Other authors support a small influence in the prevalence of Hp infection in favor of male sex [10] [27]. This is the case of the study conducted by Eisdorfer, where the influence of male sex was demonstrated in the results of the urea breath test (UBT), a test commonly used for the diagnosis of *H. pylori* infection [30]. Indeed, male sex is more associated with the risk factors for acquiring Hp infection (alcohol and active smoking) often seen in adult males [31]. However, male gender predominance was associated with a higher prevalence of *H. pylori* infection in both children and adults. This observation reinforces the contention

that the factors that might explain these differences, or affect UBT values, are not fully understood [32].

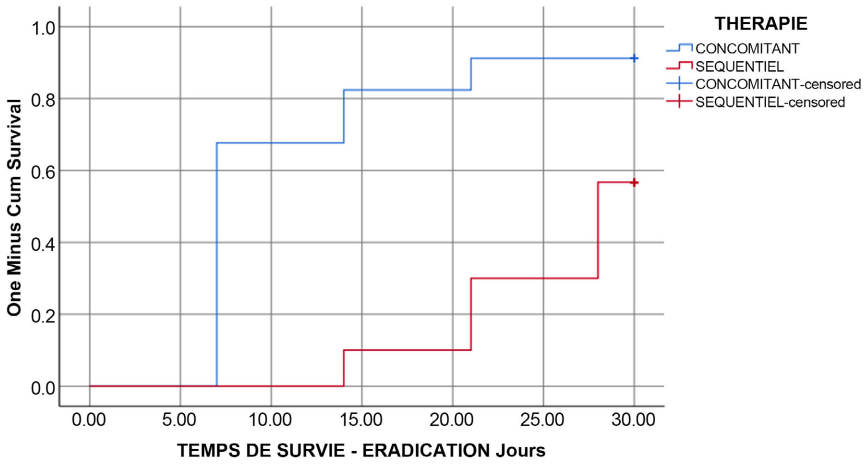

Figure 4. Survival time to eradication.

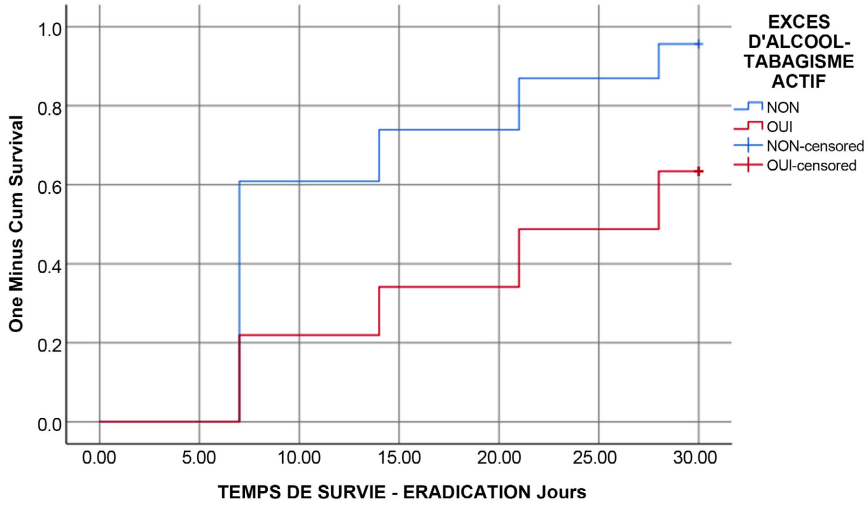

Figure 5. Survival time in relation to excess alcohol-active smoking.

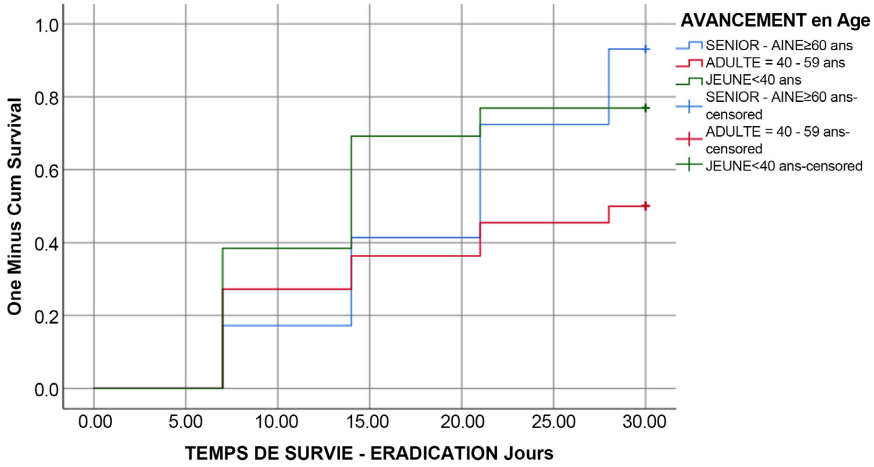

Figure 6. Survival time versus advancement in age.

In the present study, despite the 1:1 sex ratio, there was an overrepresentation of males in the study population. This may be explained by the lifestyle of men (alcohol, smoking).

4.1.2. Age

The mean age of patients with Hp infection (54.2 ± 15.1 years) in the present work reflects the preferred age of onset of symptoms of Hp infection. Indeed, the prevalence of infection in developing countries is greater than 80% in adults older than 50 years. Infected individuals usually acquire *H. pylori* before the age of 10 years and the infection peaks in adulthood, between 35 and 44 years of age [32]. It has also been shown that the seroprevalence of *H. pylori* increases with age, representing the combined effect of a decrease in the rate of exposure during childhood (associated with an improvement in the standard of living) and the acquisition of the infection with age [33], with prevalence increasing at ages above 50 years.

A study comparing the infection rates of children aged 1 to 19 years with those of adults aged 20 to 75 years found a lower prevalence in the former group (22% vs. 75%) [34]. Similarly, Mabeku *et al.* in a study conducted in Cameroon, showed that 62% of women over 68 years of age were infected with Hp [32]. Factors such as sexual intercourse, particularly fellatio, which is a very common sexual activity, can explain the high prevalence of Hp, especially in older age groups [35] [36]. Although Hp is primarily a gastric organism, studies have reported that infected individuals may carry *H. pylori* permanently or transiently in their mouth and saliva.

4.1.3. Risk Behaviors

The present study highlighted the harmful effect of excess alcohol with active smoking in the occurrence of Hp infection. Mehmet in a study that investigated the relationship between blood type, sex, age, smoking and Hp, found that there was a susceptibility of smokers to Hp compared to non-smokers [33] [37].

In previous studies, the authors have pointed out that smoking may be another factor in the sharp increase in *H. pylori* infection in persons 15 years and older [38]. In addition, it is possible that alcohol consumption, which in some studies is related to HIV status, is an indirect measure of socioeconomic and cultural variables [37].

In contrast to the present study and others conducted around the world, Olga Sjomina *et al.* [8] in a systemic review showed that there was no association between alcohols, coffee and other factors.

Similarly, Wu *et al.*, also found no association between alcohol intake and Hp infection [8] [38].

4.1.4. Treatment Modalities and Hp Infection

In general, and after several treatment regimens have been evaluated, few consistently achieve high eradication rates in first-line treatment. In addition, there are also limited data on Hp antibiotic resistance rates to guide first-line treat-

ment. However, the treatment regimen chosen should take into account local patterns of antibiotic resistance (if known), prior exposure, allergies to specific antibiotics, cost, side effects, and ease of administration [39] [40] [41]. According to some recommendations, reasonable eradication targets would be ≥90% cure rate on per-protocol analysis and ≥80% cure rate on intention-to-treat analysis [40] [42].

In the present study, successful eradication of Hp infection was more frequent in the 1-line concomitant therapy modality (91.2%; n = 31/34) than in the 1-line sequential therapy modality (56, 7%; n = 17/30). These results are in line with much data in the literature, especially for concurrent quadruple therapy [43]. However, the eradication rate in this study is much lower than the rates found in the West and in some SSA countries for four-line sequential therapy [44] [45] [46]. Although initially the 1-line sequential therapy achieved high eradication rates and was widely used in Italy [44], its efficacy has decreased over time influenced by resistance to clarithromycin and metronidazole [21] [46].

A systematic review and meta-analysis reported that rates of primary and secondary resistance to clarithromycin, metronidazole, and levofloxacin exceeded 15% (alarming levels) in all World Health Organization (WHO) regions [21] [47] [48] [49].

As a result, in 2017, clarithromycin-resistant *H. pylori* were defined as a high-priority bacterium in the WHO priority list of antibiotic-resistant bacteria [50].

The modality of sequential treatment, which does not allow maximizing the synergy of the different antibiotics used, may explain this low eradication rate. However, Zullo *et al.* [45] reported that sequential treatments of 10 and 14 days achieved treatment success (above 90% according to PP analysis) for first-line *H. pylori* eradication in clinical practice in Italy. In Korea, where antibiotic resistance rates are relatively high, the efficacy of 10-day sequential therapy was reported at 76.3% and 85.0% on an intention-to-treat (ITT) and perprotocol (PP) analysis, respectively. These results were described as unsatisfactory [51].

Concomitant therapy contains three antibiotics and a PPI; its eradication rate is not compromised by resistance to clarithromycin or metronidazole, unless there is dual resistance [13].

A prospective study in Greece showed that eradication rates of concomitant therapies were above 90% by PP analysis and well tolerated. However, 31.3% of treated patients had side effects [52].

4.1.5. Predictors of Successful Eradication of *Helicobacter Pylori* Infection

Several factors influence the outcome of eradication therapy for Hp infection. A study in South Korea showed that resistance to clarithromycin alone or in combination with metronidazole resistance (dual resistance) significantly reduced the eradication success rate after sequential treatment. However, double resistance did not affect the eradication rate after concurrent treatment [53]. Other factors may also explain the propensity for low success with sequential therapy.

In particular, major adverse events were defined as predictors of eradication in the sequential group. Adherence to treatment had a significant influence on the efficacy outcome in the concurrent treatment group [53].

As described in some studies [32] [54] [55], excess alcohol with active smoking had a deleterious effect in the occurrence of Hp infection. Indeed, it has been reported in the literature that metronidazole produces a disulfiram-like reaction (vomiting, nausea, dizziness) when taken in combination with alcohol with the possibility of negatively influencing the success rate of sequential treatment, especially since the adverse effects are no longer observed in this type of therapeutic scheme.

A meta-analysis showed that smoking increased the treatment failure rate for *H. pylori* eradication [54] [55]. Similarly, a multivariate logistic regression analysis showed that smokers had a 2-fold higher probability of failure in *Helicobacter pylori* eradication than nonsmokers (OR: 2.0; 95% CI: 1.01 - 3.95) [55]. However, lifestyle factors, including smoking and alcohol consumption, did not worsen *H. pylori* eradication failure in the study by Suzuki *et al.* [56].

Several studies have investigated the impact of age on the success of eradication of Hp. [57] [58] [59] [60] [61]. In a Chinese study, age was found to be associated with *H. pylori* eradication. Indeed, the eradication rate was higher in patients ≥ 40 years of age than in patients < 40 years of age (85.7% vs. 54.7%, P = 0.002). In addition, the eradication rate was 100% in patients older than 60 years [57]. Japanese authors also found a relationship between eradication failure and being in the under-50 age group [59] [60] [61]. These results are in line with the present study which showed that advancing age was a predictor of successful eradication of *H. pylori* infection. This is thought to be related to the fact that the gastric mucosa of advanced age is more atrophic than that of younger patients and therefore secretes less acid than normal mucosa [57] [59]. The ability of gastric acidity to decrease the effectiveness of antibiotics is, therefore, less important in older people than in younger subjects [59].

4.1.6. Strengths and Limitations of the Study

The present study presented strengths balanced by some degree of limitations.

The strength of this study lies in its originality. Indeed, it is the first study in Kinshasa to have investigated the eradication rate of sequential and concomitant quadritherapies in patients with Hp infection.

However, the weaknesses of this study are inherent in its secondary and documentary nature, which is often characterized by biases in the completeness of information, as well as in its sample size, which did not allow certain conclusions to be drawn. Thus, an analytical study with a larger sample size would be needed to investigate other variables and to look for determinants and/or predictors of Hp eradication rates not analyzed in this study.

It would be interesting to subject patients who have failed first-line therapy to second-line therapy and to evaluate its efficacy; as well as to study the efficacy of other therapeutic modalities such as hybrid triple therapy and hybrid reverse

therapy which give eradication rates in ITT and PP of 97.5% and 100% respectively [62].

4.1.7. Implications

The current results will have implications for routine practice, pharmacovigilance, capacity building, and public health perspectives related to Hp infection in DRC. In addition, they will serve as a database for future large-scale studies.

5. Conclusion

The present study showed the superiority of the concomitant quadruple therapy compared to the sequential quadruple therapy. It also underlined the negative influence of alcohol with active smoking and the positive influence of quadruple therapy and advancement in age in the success of eradication of *Helicobacter pylori* infection, a prevalent problem in the DRC in general and in Kinshasa in particular.

Authors' Contributions

PNK AND FA initiated the study; PNK, AOBM, ATY, TMM participated in the study design; AOMB, MSNN, PNK, TMM wrote the manuscript; FA, PNK, TK, AOBM, supervised data collection; BLM validated and analyzed the data; BLM, BMK, AOBM, and MSNN interpreted the data; all authors made intellectual contributions to the draft manuscript and approved the final manuscript for submission.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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