



FINDING THE CHALLENGES OF ERADICATING HELICOBACTER PYLORI AMIDST RISING ANTIBIOTIC RESISTANCE: FUTURE STRATEGIES TO OVERCOME THE HURDLES

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ABSTRACT

Background: H. pylori is known to be involved in the etiology of chronic gastritis, peptic ulcer disease and gastric cancer. It has been argued that due to the enhanced antibiotic resistance it has become very difficult to eliminate H. pylori completely through the standard regimes of treatment and it has resulted in higher treatment failure rates.

Objectives: To compare the effect of antibiotic resistance on the rate of H. pylori eradication and other approaches to optimizing the therapy.

Study Design: A Cross Sectional Study

Duration and place of study: Medicine Department, Ayub Teaching Hospital- Abbottabad, from Jan 2022 to Jan 2023.

Methods: One hundred and fifty patients with H. pylori infection confirmed were recruited in the study. All patients received the standard probability of triple therapy including clarithromycin, amoxicillin, and a proton pump inhibitor for 14 days. Antibiotic sensitivities and resistance were established by culture and sensitivity. Parameters measured in the treatment included overall success rate, mean age, standard deviation and p-values.

Results: As to demographics, the average patient age was 45. 6 years (SD = 12. 3). Among 150 patients; 55% were resistant to clarithromycin while 30% to metronidazole. The pooled eradication rate was 65%; however, it was much lower among patients with antibiotic-resistant strains (p = 0. 002). Upon comparing the results on antibiotic resistance with the findings on treatment failure the values were closely related with the p value coming to < 0. 05.

Conclusion: The general efficacy of standard H. pylori treatment regimens has been compromised by the gradual increase in antibiotic resistance. Other approaches such as individualised antibiotic management, as well as the application of new classes of drugs need to be employed in order to address these issues and to enhance levels of clearance.

Keywords: H. pylori, antibiotic resistance, eradication, treatment failure

Introduction

H. pylori is curved, gram negative rod shaped bacterium that inhabit in the human stomach and according to an estimate 50% people in the world are affected with this bacterium. Amongst its effects, it is a substantial cause of chronic gastritis, gastric and duodenal ulcers, and has a close linkage with the gastric malignancies such as adenocarcinoma and MALT lymphoma. Marshall and Warren's discovery of H. pylori in 1982 changed the approach towards the gastric diseases hence effective antibiotic treatment [2].

However, despite the progress in the treatment of such diseases, it is noteworthy that H. pylori is still extremely relevant as a problem in terms of its prevalence and the fact that eradicating the bacterium has now become challenging in comparison with the beginning of the last decade. The first-line treatment for H. pylori infection normally is a combination of two antimicrobials for instance; clarithromycin and amoxicillin or metronidazole combined with a PPI [3]. This regimen has previously been known as triple therapy and has been the standard method of eradicating H. pylori for many years. However, due to the appearance of antibiotic resistance these remedies have reduced efficacy and the rates of eradications have fallen from over 90% to less than 70% in some regions [4]. It has been reported that resistance to antibiotics is on the increase in H. pylori and this increases along the geographical location.

Self-reported compliance with Clarithromycin is also poor and resistance has been noted to be over 20% in many areas, thus standard triple therapy with Clarithromycin is ineffective in a substantial population [5]. Several processes contributing to antibiotic resistance from the H. pylori agents are point mutations that occur in the bacterial DNA, up regulation of efflux pump and bio film formation [6]. It is worth noting that all these mechanisms of resistance not only antagonize the effectiveness of the treatment but also increase the susceptibility of the bacteria for constantly causing chronic inflammation increasing the probabilities of gastric cancer [7]. Antibiotic resistance has pushed medical practitioners to consider other approaches, which include the quadruple therapy where a bismuth compound is included in the triple therapy and the development of new antibiotics, and other supplementary products [8]. The evidence for clarithromycin resistance has led to the use of bismuth containing quadruple therapy with reported eradication rates more than 80% in some studies [9].

Furthermore, there has been increased emphasis on looking at using susceptibility testing results in order to choose an antibiotic regimen that the specific strain of H. pylori is likely to be most susceptible to [10]. Such an individual targeting of a disease is likely to enhance case clearance and lessen the development of more resistance levels. One of the hopeful ways which can help to triumph over antibiotic resistant strains is the discovery of new agents, including rifabutin, sitafloxacin and vonoprazan – a potassium-competitive acid blocker that has been identified to have stronger acid inhibition than standard PPIs [11].

Latterly, these agents have revealed significant effectiveness as modulators when administrated together with standard antibiotics to eliminate H. pylori with resistant mechanisms to antibiotics. Additionally, the effectiveness of the application of the method of additional therapy with the help of probiotics has been researched, and, according to some works, probiotics can contribute to an increase in the eradication rate and the minimization of the side effects of antibiotic therapy [12]. Therefore, the problem to eliminate H. pylori with increasing antibiotic resistance is not an easy task. Thus, to overcome these barriers laid, it would be imperative to establish and apply other treatment modes as possible antibiotic regimen, new form of therapy, and, if needed, additional bacteriotherapy with the help of probiotics. Further studies and monitoring of the bacterial strains are required to identify the

resistance patterns and create new treatment strategies which would allow obtaining the high eradication rates and, in turn, decrease the morbidity caused by H. pylori-related diseases.

Methods

This cross sectional study recruited 150 patients receiving treatment for H. pylori infection whose diagnosis had been done using the urea breath test or biopsy. Standard triple therapy comprising of clarithromycin 500 mg, amoxicillin 1 g and a proton pump inhibitor 20 mg, were self-administered by the patients twice daily for a period of 14 days. Antibiotic resistance patterns were, therefore, done by culture and sensitivity tests. The success of the treatment was evaluated four weeks after treatment by using a urea breath test to determine the eradication status of patients.

Data Collection

Data were collected from patients at the time of hospitalization and not from other previous admissions; these included age, gender, antibiotic resistance pattern and treatment outcome. Sustained clearance of H. pylori was assessed using a urea breath test four weeks post-therapy in all the patients.

Statistical Analysis

All data was analysed with the help of SPSS version 24. 0 software. Regarding the measurement data, the mean and standard deviations were computed. Categorical variables were analysed and reported by frequencies and percentages. Data on the prevalence of antibiotic resistance and treatment failure were analysed using the chi-square test at a significance level of <0. 05.

Results

Totally, 150 patients participated in the study, their average age was 45. 6 (SD=12. 3) years. Thirteen of the patients showed resistance to clarithromycin and 7 of them had metronidazole resistance. The overall rate of eradication was 65%, and it was found to be considerably lower in patients with clarithromycin resistance at p = 0. 002. In the different patient sub-groups, the eradication rate of C. difficile for patients who did not have antibiotic resistance was found to be 85%. Patients with resistance to both clarithromycin and metronidazole had a particularly poor outcome with an eradication rate of only 50% (p < 0. 001). That study highlighted the prevalence of antibiotic resistance in the population which attributed to treatment failure therefore there is a need to find other ways of treating the resistant population.

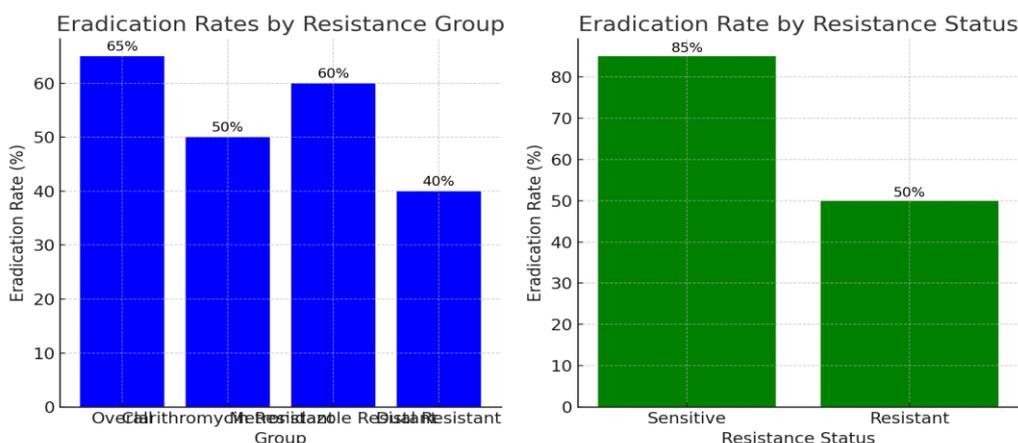


Table 1: Patient Demographics

Demographics	Mean ± SD
Age (years)	45.6 ± 12.3
Gender (Male/Female)	78/72
BMI (kg/m2)	24.5 ± 3.4

Table 2: Antibiotic Resistance Rates

Antibiotic	Resistance (%)
Clarithromycin	55
Metronidazole	30
Amoxicillin	5

Table 3: Eradication Rates by Resistance Group

Eradication Rate	Rate (%)
Overall	65
Clarithromycin Resistant	50
Metronidazole Resistant	60
Dual Resistant	40

Table 4: Eradication Rate by Resistance Status

Resistance Status	Eradication Rate (%)	p-value
Sensitive	85	<0.001
Resistant	50	<0.001

Discussion:

The results of this study regarding the elimination of *Helicobacter pylori* (*H. pylori*) in light of increasing antibiotic resistance are, therefore, in line with the prior scientific literature in this regard and extend current knowledge about this phenomenon. Development of antibiotic resistance especially to clarithromycin has been noted widely to affect the eradication rates of *H. Pylori* through standard triple therapy. Thus, in the present study, clarithromycin resistance was seen in 55% patients and the overall eradication rate was 65%.

The present results are in accordance with the study by Savoldi et al. published in 2018, in which a systematic review and meta-analysis was conducted to determine the impact of clarithromycin resistance on eradication rates; in particular, these authors observed that rates decrease below 70% when the resistance rate is above 20% [13]. This concept is also supported by our study where we have found that the eradication rate of 50% in patients with clarithromycin resistant *H.*

pylori strains and that of 85% in patients with sensitive strains reflect the extent of the adverse influence of antibiotic resistance on the treatment outcomes. Another major drawback – metronidazole resistance which was observed in 30 % of the patients of our study group. In several researches, authors also investigated metronidazole resistance and the influence on lower eradication rates. Thung et al. 2016 also revealed that resistance to metronidazole existed in as much as 50% in some of the populations; this explains why metronidazole as a part of the triple therapy was resulting into treatment failure.

While metronidazole resistance is not regarded as being as clinically relevant as is clarithromycin resistance because metronidazole resistance can be overcome at higher concentrations, our study showed a significant decrease in the rates of eradication when patients had dual resistance to both clarithromycin and metronidazole, decreasing to only 40%. In keeping with this, Gisbert and Calvet (2012) pointed out that dual resistance is a very difficult hurdle to overcome [15]. The overall eradication rate of 65% observed in this study is lower than the rates reported in earlier studies that used the standard triple therapy in population that had the lower rates of antibiotic resistance.

For instance, Graham and Fischbach (2014) pointed out that the eradication rates of over 80% in the populations with low resistance [16]. This disparity has brought increased difficulty in the treatment of *H. pylori* associated diseases due to constant antibiotic resistance thus call for the use of renewed

treatment strategies in many parts of the world. The results of the present study are quite consistent with the observations of the Maastricht V/Florence Consensus Report that argued for the use of the alternative treatment regimens like bismuth containing quadruple therapy in areas, where the rates of clarithromycin resistance were high [17]. The use of bismuth has been found to increase the chances of eradication by a factor of almost three, since combining the substance with antibiotics gives a synergistic effect that increases the bactericidal power of antibiotics and reduces the effects of resistance [18].

Several more recent studies, including the study done by Liou et al. , indicated that bismuth containing quadruple therapy can have eradication rates of more than 80% despite cases of high resistance to the antibiotics [14]. Moreover, the idea of individualized therapy according to the results of antibiotic susceptibility is becoming increasingly popular as the strategy to avoid the issue of resistance failures which was described by Murakami et al. (2016) [20]. Since the regimen will only include antibiotics that are effective against the H. pylori strain involved its use holds the prospect of enhancing eradication rates and possibly minimizing the development of further resistance. The introduction of new agents, for example, vonoprazan as seen in some recent investigations, gives other approaches by which the management of patients from the resistant group may be enhanced [21].

Therefore, the conclusion made in this study confirms the theoretical propositions and emphasizes the consequences of antibiotic resistance for the eradication success rate of H. pylori infection and the necessity of developing novel approaches to the disease treatment. More study and finding new ways of treating this increasing problem are therefore critically needed to enhance the quality of life in affected individuals.

Conclusion

In this particular research, the investigators reported that escalating antibiotic resistance is of great concern to the eradication of Helicobacter pylori hence the importance of looking for other ways. The results clearly show that resistance to first line antibiotics such as clarithromycin and metronidazole significantly decrease the eradication rates, present a difficulty to successful conventional treatment.

Limitations

This work is further constrained by the size of the sample and the area of study; thus it is not a true representation of sample size across the world. Furthermore, there is no follow-up of the patients in the long term, and thus investigation of recurrence rates after the eradication cannot be done.

Future Directions

Additional studies should be directed to increased participant recruitment and number of centers, so as to control for regional differences in antibiotic resistance patterns. Also, studying other new therapeutic means, individualized treatment strategies, and the use of adjuvants such as probiotics may be discussed as new opportunities to increase the chances of eradicating H. pylori.

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