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Is Hybrid therapy more efficient in the eradication of Helicobacter pylori infection? A systematic review and meta-analysis.

REVISÃO SISTEMÁTICA E META-ANÁLISE

ÁREA CIENTÍFICA DE GASTROENTEROLOGIA

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Is Hybrid therapy more efficient in the eradication of *Helicobacter pylori* infection? A systematic review and meta-analysis.

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ABSTRACT

Introduction: Hybrid therapy (HT) is a non-bismuth quadruple therapy created to surpass *Helicobacter pylori*'s (Hp) resistance rates to antibiotics. HT has excellent eradication rates, as well as an excellent compliance and safety profile. We aim to compare HT with sequential therapy (ST) and concomitant therapy (CT) for the eradication of Hp.

Methods: This systematic review was conducted following the principles of the PRISMA 2015 guidelines. Literature was electronically searched on the CENTRAL library, PubMed, Scopus, LILACS, and ClinicalTrials.gov. Only randomized controlled trials were included. Primary outcome evaluated was eradication rate of Hp. The secondary outcomes evaluated were adverse effects and compliance rates. Meta-analyses were performed with Cochrane Review Manager 5.4. The Mantel-Haenszel method was used to estimate the pooled relative risk and 95% CI of the eradication rates between HT and other eradication therapies, as well as the secondary outcomes.

Results: 10 studies were included, including 2993 patients. The mean eradication rates achieved by HT with intention-to-treat (ITT) and per-protocol (PP) analyses were, respectively, 86% (range: 79.2-90.8%) and 91.7% (range: 82.6% to 96.1%). No statistically significant difference was found in ITT eradication rate between HT and CT (relative risk: 1; 95% CI: 0.96, 1.03) and between HT and ST (relative risk: 1.02; 95% CI: 0.92, 1.14). PP analysis showed similar results. HT was associated with higher compliance rates than CT, but lower than ST (95.7% Vs 93% Vs 97.3%, respectively). As far as adverse events are concerned, this meta-analysis revealed a slightly higher occurrence of adverse events on the group of patients treated with HT (30.7% Vs 26% Vs 38.9%). These differences were not statistically significant.

Conclusion: HT has similar eradication, compliance and adverse event rates when compared to sequential and concomitant regimens.

Keywords: *Helicobacter pylori*; hybrid therapy; concomitant therapy; sequential therapy; eradication rates.

LIST OF ABREVIATIONS

CASP-RCT – Critical Appraisal Skills Programme – Randomized Clinical Trials

CI – confidence interval

CT – concomitant therapy

Ct – culture

HA – histological assessment

Hp – *Helicobacter pylori*

HT – hybrid therapy

ITT – intention-to-treat

LILACS – Latin American and Caribbean Centre on Health Sciences Information

MALT – mucosa-associated lymphoid tissue

PICO – Population; Intervention; Comparison; Outcome

PP – per-protocol

PPI – proton pump inhibitor

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-analyses

PROSPERO – International Prospective Register of Systematic Reviews

RCT – randomized clinical trial

RR – risk ratio

RUT – rapid urease test

SAT – stool antigen test

ST – sequential therapy

UBT – urea breath test

INTRODUCTION

Helicobacter pylori (Hp) infection is one of the most prevalent infections worldwide. As a matter of fact, approximately 50% of the world's population is infected with Hp (1). This microorganism plays an essential role in the pathogenesis of many gastroduodenal diseases, including chronic gastritis, peptic ulcer disease, low grade mucosa-associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma (2). In fact, Hp is one of the most important carcinogenic factors contributing to gastric cancer and this malignancy is the third leading cause of cancer-related death worldwide (3). This bacterium may also contribute to the physiopathology of functional dyspepsia, but this data is still to be completely determined (4). Recent studies have revealed that Hp eradication leads to lower rates of gastric cancer. This fact makes finding the best therapy to Hp an urgent necessity (5,6).

Even though this bacterium's discovery took place more than 20 years ago (7), there are still major challenges regarding its eradication (8). The most successful treatment regimen is yet to be determined. The four most used antibiotics in this treatment are: metronidazole, clarithromycin, amoxicillin, and tetracycline (4). This fact results from the efficacy of these therapies and relatively low rates of side effects. Nevertheless, recently, there has been a rise in bacterial resistance to these therapies: firstly, to metronidazole and later to clarithromycin. As a result, treatment must include more than one antibacterial mechanism of action, to obtain an effective result (7,9). The already purposed regimens are: Triple therapy (proton pump inhibitor (PPI) and two antibiotics, clarithromycin and amoxicillin or metronidazole), non-bismuth quadruple therapy (PPI, clarithromycin, metronidazole, and amoxicillin) and bismuth quadruple therapy (PPI, bismuth salt, tetracycline, and metronidazole) (10). Efficacy of triple therapy, the first proposed regimen, has been declining as resistance rates are evolving (11). As a matter of fact, previous works have outlined that efficacy of this regimen is manifestly insufficient. (12–14).

The major challenge in the eradication of Hp lies on antibiotic resistance. Indeed, this obstacle is the main cause of treatment failure. Bacterial gene mutations seem to play a major role in the resistance (10). In many countries, primary clarithromycin and metronidazole resistance rates are higher than 15%, and primary combined resistance rates to clarithromycin and ins10% (15). In Portugal the resistance rates are as high as 40-50% to clarithromycin and around 25-30% to metronidazole (16,17).

Understandably, the high rates in antimicrobial resistance hinder the efficacy of treatment regimens, resulting in the decrease of this parameter to unacceptable values, ranging from 70-80% in triple therapy and about 80% in quadruple treatment regimen (7,10). Moreover, the

therapy regimens currently used can vary in efficacy, with the sequential therapy (ST) having lower eradication rates compared to its counterparts, due to antimicrobial resistance (2).

Hybrid therapy (HT) is a quadruple non-bismuth therapy, which functionally is a combination of sequential and concomitant therapies. HT consists of a proton pump inhibitor (PPI) and amoxicillin for 10 to 14 days, adding clarithromycin and metronidazole in the final 5 to 7 days of treatment. The original clinical trial demonstrated an eradication rate of 99.1% (95% confidence interval (CI): 97.3%-100.9%) according to per-protocol (PP) analysis and 97.4% (95%CI: 94.5%-100.3%) by intention-to-treat (ITT) analysis (18,19). According to these findings, HT seemed promising.

In recent years, HT has been gaining attention as a potentially more successful therapy, showing better results eliminating this bacterium compared to other treatment regimens in several clinical trials (9). Nevertheless, the conclusions of the studies were not consensual. Some randomized clinical trials revealed conflicting results, not being concordant on whether HT was better at eradicating Hp than ST (20–23).

Knowing the most efficacious therapy regimen is an imperative since Hp infection is responsible for losses in health-related quality of life and to deaths worldwide. We thus aim to compare the effectiveness of the HT in the eradication of Hp with other recommended therapeutic regimens: sequential, concomitant, and triple therapies. Moreover, we aim to compare the adverse effects and compliance rates between the above-mentioned therapies will be included.

METHODS

Protocol and Registration

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (24).

The protocol of the present review was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database under the identification number CRD42022314599.

Eligibility criteria

To define our eligibility criteria, we referred to the PICO (Population; Intervention; Comparison; Outcome) framework, according to the current PRISMA guidelines.

Our population was defined as adults (older than 18 years-old) who were diagnosed with a Hp infection, with or without dyspeptic symptoms. Hp infection diagnostic methods were defined as follows: endoscopy with biopsies of the stomach, with either histological examination, gram staining or rapid urease test; urea breath test and/or stool antigen test.

The intervention in this study was the HT, defined as the administration of any PPI at any dose for 10 to 14 days twice daily; plus, amoxicillin 1000mg for 10 to 14 days twice daily; plus, the addition of clarithromycin 500mg or moxifloxacin 400mg twice daily and metronidazole tinidazole 500mg twice daily in the final 5 to 7 days of the treatment.

HT is being compared to other non-bismuth therapies (control groups) used in the treatment of Hp infection: concomitant therapy (CT) and sequential therapy (ST).

CT included patients take any PPI at any dose, amoxicillin 1000mg, clarithromycin 500mg or moxifloxacin 400mg and metronidazole or tinidazole 500mg all twice daily for 10 to 14 days. (Figure 1).

ST, defined as taking any PPI at any dose twice daily for 10 to 14 days, plus amoxicillin 1000mg twice daily in the 5 to 7 initial days of therapy, followed by clarithromycin 500mg or moxifloxacin 400mg and metronidazole or tinidazole 500mg twice daily in the last 5 to 7 days of therapy. (Figure 1).

HT scheme		
PPI	10-14 d	
amoxicilin	10-14 d	
clarithromycin		5-7 d
metronidazol		5-7 d

ST scheme		
PPI	10-14 d	
amoxicilin	5-7 d	
clarithromycin		5-7 d
metronidazol		5-7 d

CT scheme	
PPI	7-14 d
amoxicilin	7-14 d
clarithromycin	7-14 d
metronidazol	7-14 d

Figure 1: Therapeutic schemes of Hybrid, Sequential and Concomitant regimens, respectively.

An acceptable eradication rate was defined as equal or higher than 90%, as defended by Graham D. (25). Assessment of Hp eradication was performed 4 to 6 weeks after treatment, using either urea breath test (UBT), histologic assessment (HA) by biopsy with or without rapid urease test (RUT), or stool antigen test (SAT).

Additional outcomes of this review were the comparison of compliance rates and adverse events between the intervention and control groups.

Information sources and search strategy

The literature was searched electronically on the Cochrane Central Register of Controlled trials library, PubMed, Scopus, LILACS, and ClinicalTrials.gov. The search term ((helicobacter pylori) AND (hybrid therapy)) was used across all platforms.

Only randomized controlled trials were included. Only articles written in the English language were included. The latest update on the search was performed on May 7, 2021. All studies published before this date were included. The detailed search strategy is illustrated in figure 3. References of the studies reviewed were also searched to avoid any exclusion.

Study selection

The study selection was comprised of two screenings, performed independently by two reviewers (DJM and MJT). Reviewers assessed the abstracts and titles of the articles and the articles that were deemed highly unlikely to be relevant to the study were excluded. Next, the two reviewers assessed the full-text articles, screening for inclusion criteria according to our defined PICO.

Studies in children, reviews and meta-analysis, reports, letters, editorials, basic research, studies in animals and abstracts with insufficient information were excluded.

The study appraisal was conducted using the Critical Appraisal Skills Programme – Randomised Controlled Trials (CASP-RCT) checklist (26).

Data collection process and data items

The data extracted included: study design; length of follow-up; patients' demographics, patients' symptoms (when applicable); diagnostic methods; number of enrolled participants in the study; number of participants in each group; therapies used in the different groups and their respective dosages; eradication rates (ITT and PP analysis); adverse effects and compliance rates of the groups.

Risk of bias assessment

Risk of bias of the included articles was assessed independently by two reviewers (DJM and MJT), using the Review Manager (RevMan) version 5.4. The Cochrane Collaboration, 2020. In case of any discrepancies, the reviewers discussed until a consensus was reached. The risk of bias assessment is summarized in figure 2.

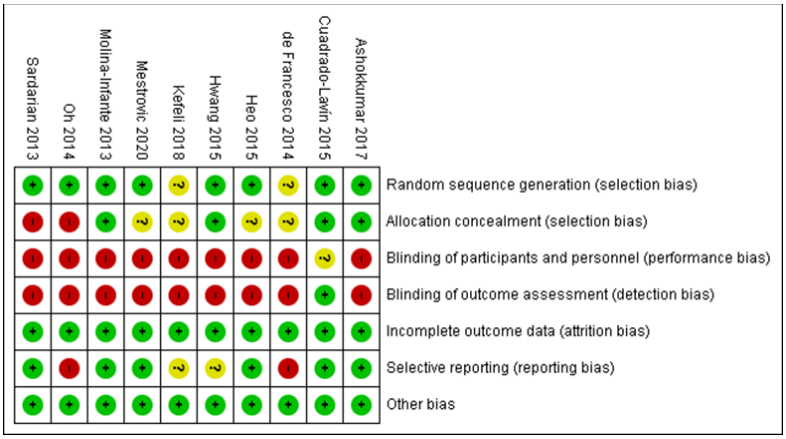

Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Statistical Analysis

Statistical analysis was performed using Review manager 5.4 from the Cochrane Collaboration, computing meta-analysis of the studies for the endpoints defined (eradication rates, adverse effects, and compliance rates).

The measure of effect considered was the risk ratio favouring HT versus CT and HT versus ST, and its 95% confidence interval was estimated by the Mantel-Haenszel method using a random effects model. The statistical significance of the overall effect was assessed by the Z-statistic approximation and its p-value, interpreted at a 5% significance level. Heterogeneity between studies was evaluated by the Thompson and Higgins statistics and was quantified using the I^2 statistics.

RESULTS

Study selection and characteristics

The research that was conducted resulted in 94 entries across the five databases. All 94 records were first screened by two authors (DJM and MJT), who assessed their titles and abstracts. 59 studies were excluded either because they did not include HT but included reverse hybrid therapy; they did not compare hybrid therapy to sequential or concomitant therapies; abstracts were not available in the English language. The remaining 35 full texts were retrieved and assessed for our defined eligibility criteria, and finally we identified a total of 10 studies that met our eligibility criteria. The study selection process is described in accordance with the PRISMA methodology and is illustrated in figure 3. A summary of the general characteristics of the included studies is shown in table 1.

Table 1: Summary of the included studies

			Sample Size				Diagnosis Methods	
Publication Year	**First Author**	**Country**	**Study Design**	**HT**	**Controls**	**Total Enrolled**	**Patient Characteristics**	**Infection diagnosis**	**Eradication**
2020	Antonio Mestrovic	Croatia	RCT	71	69	140	Dyspeptic symptoms	SAT, RUT, UBT, HA	SAT
2015	Jun Heo	Korea	RCT	241	209	422	Dyspeptic symptoms	RUT, UBT or HA	UBT
2015	Jae Jin Hwang	Korea	RCT	144	140	284	Gastritis and/or Peptic Ulcer Disease	UBT, HA, RUT	UBT
2014	Vincenzo De Francesco	Italy	RCT	110	330	440	Dyspeptic symptoms	RUT and HA	UBT
2013	Hossein Sardarian	Iran	RCT	210	230	420	Gastric or Duodenal Erosions	HA and/or RUT	UBT
2014	Dong Hyun Oh	Korea	RCT	90	94	184	Dyspeptic symptoms	RUT or HA	UBT
2013	Javier Molina-Infante	Italy + Spain	RCT	171	172	343	Dyspeptic symptoms	UBT, RUT, HA or Ct	UBT
2015	Antonio Cuadrado-Lavín	Spain	RCT	120	180	300	Dyspeptic symptoms	UBT, HA or RUT	UBT
2018	Ayşe Kefeli	Turkey	RCT	170	170	340	Gastritis	HA	UBT
2017	Sahoo Ashokkumar	South India	RCT	60	60	120	Gastritis and/or Peptic Ulcer Disease	HA	HA or RUT

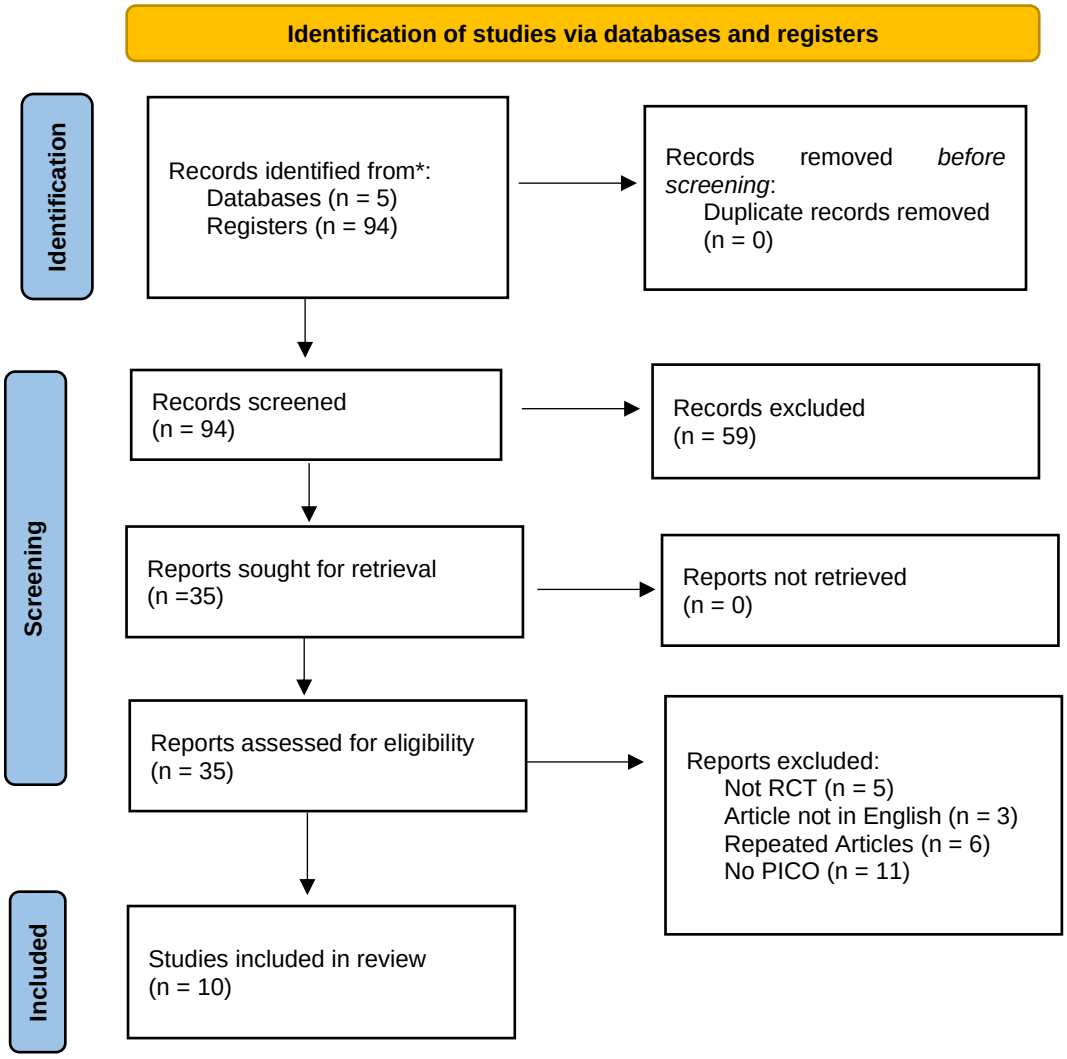

Figure 3: Study selection flowchart.

Overall eradication rates, adverse effects, and compliance rates

The mean eradication rates achieved by HT with ITT and PP analyses were, respectively, 86% (range: 79.2 to 90.8%) and 91.7% (range: 82.6% to 96.1%). Adverse events were 30.7% (range: 12.8% to 67.5%), 26% (range: 11.8% to 43%) and 38.9% (range: 14.05% to 65.8%) in HT, ST, and CT groups respectively. Regarding compliance rates, HT showed an average of 95.7% (range: 87.3% to 100%); ST had an average of 97% (range: 95% to 100%) and CT had an average of 93% (range: 87% to 98%).

Hybrid therapy versus Concomitant therapy

HT and CT were compared across 5 studies (21,27–30), including a total of 1471 patients. According to ITT analysis, the differences in eradication rates between these groups were not statistically significant (RR 1 [0.96, 1.03], p = 0.80, I^2 = 0%) (Figure 4). PP analysis showed similar results, demonstrating thar eradication rates did not statistically differ between HT and CT (RR 1.01 [0.97, 1.05], p = 0.70, I^2=46%) (Figure 5).

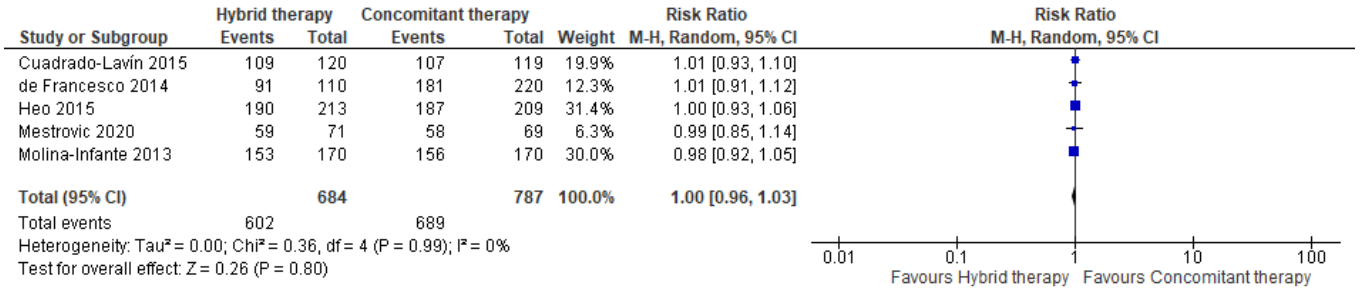

Figure 4: Forest plot comparing eradication rates of Hybrid therapy and Concomitant therapy (intention-to-treat analysis) in the treatment of *Helicobacter pylori*.

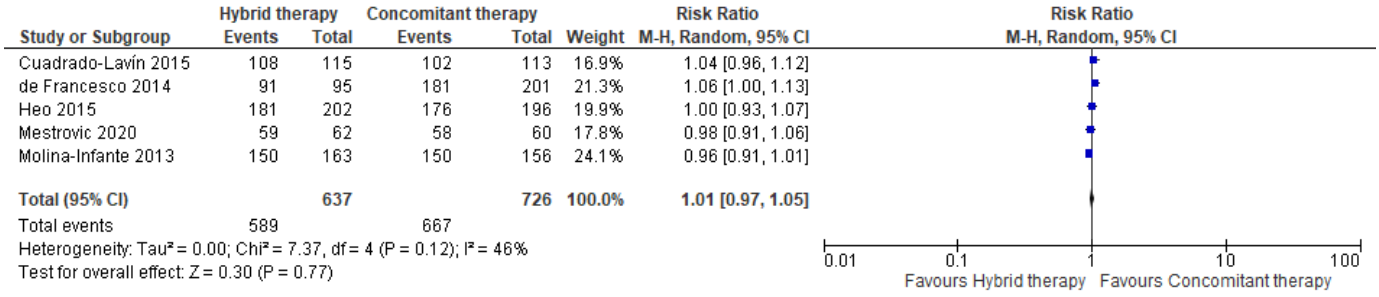

Figure 5: Forest plot comparing eradication rates of Hybrid therapy and Concomitant therapy (per-protocol analysis) in the treatment of *Helicobacter pylori*.

Regarding adverse events, the meta-analysis did not show a statistically significant difference between HT and CT, when including all five studies and with a statistically significant high heterogeneity among the groups (RR 0.95 [0.72, 1.25], p = 0.70, I^2 = 67%). When analysing data omitting Cuadrado-Lavín et al (27) from the pool of studies, I^2 became 0%, and the difference in adverse effects occurrence between the groups became statistically different,

demonstrating a risk reduction of 17% in HT group (RR 0.83 [0.71, 0.98], p = 0.03, I^2 = 0%) (Figures 6 and 7).

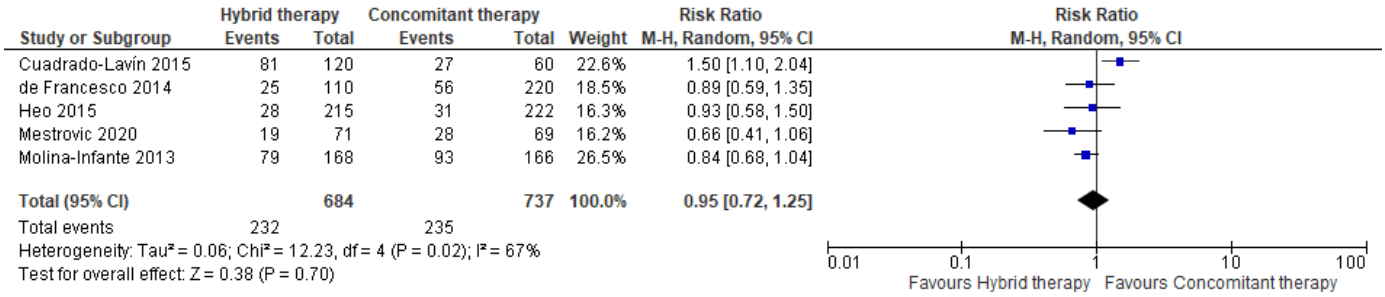

Figure 6: Forest plot comparing adverse events of Hybrid therapy and Concomitant therapy in the treatment of *Helicobacter pylori*.

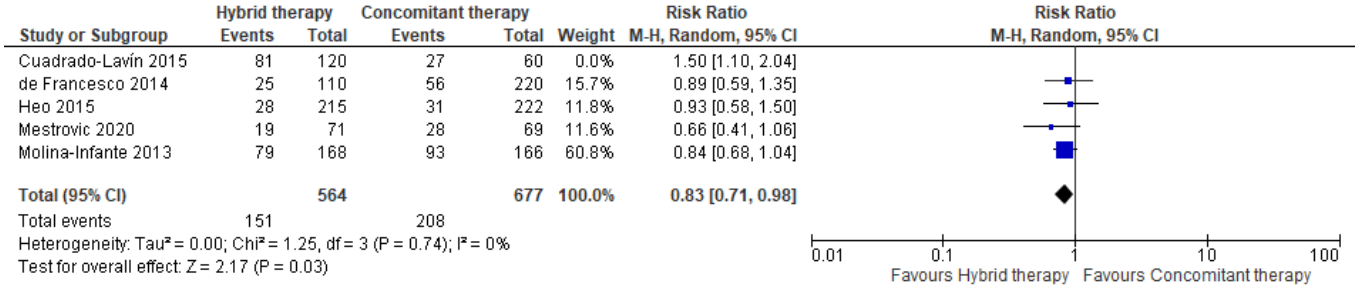

Figure 7: Forest plot comparing adverse events of Hybrid therapy and Concomitant therapy in the treatment of *Helicobacter pylori* (fixed for heterogeneity).

The difference in compliance rates between the groups was statistically significant, favouring HT and indicating a higher chance of compliance by 3%, compared with CT (RR 1.03 [1.0, 1.05], p = 0.04, I^2 = 0%) (Figure 8).

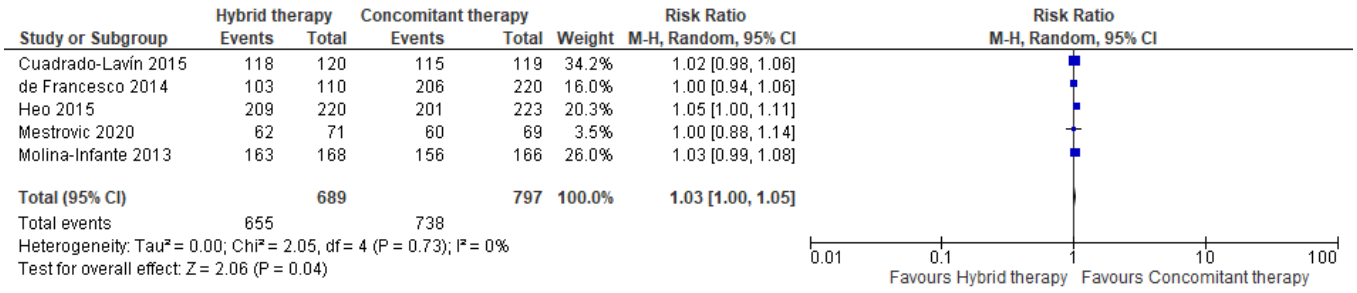

Figure 8: Forest plot comparing compliance rates of Hybrid therapy and Concomitant therapy in the treatment of *Helicobacter pylori*.

Hybrid therapy versus Sequential therapy

HT and ST were compared across 6 studies (21,22,31–34), reporting on a total of 1568 patients. When it comes to eradication rates according to ITT, the meta-analysis showed significant heterogeneity between the groups, but no statistically significant difference in this outcome (RR 1.02 [0.92, 1.14], p = 0.66, I^2 = 82%) (Figure 9). When analysing for PP, the results were similar, demonstrating a high heterogeneity between the groups and no statistically significant difference between HT and ST (1.04 [0.96, 1.12], p = 0.34, I^2 = 80%) (Figure 10).

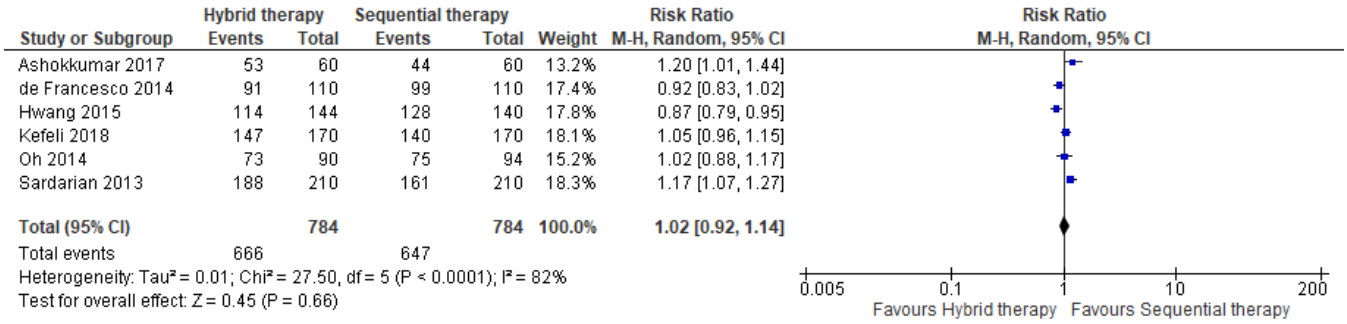

Figure 9: Forest plot comparing eradication rates of Hybrid therapy and Sequential therapy (intention-to-treat analysis) in the treatment of *Helicobacter pylori*.

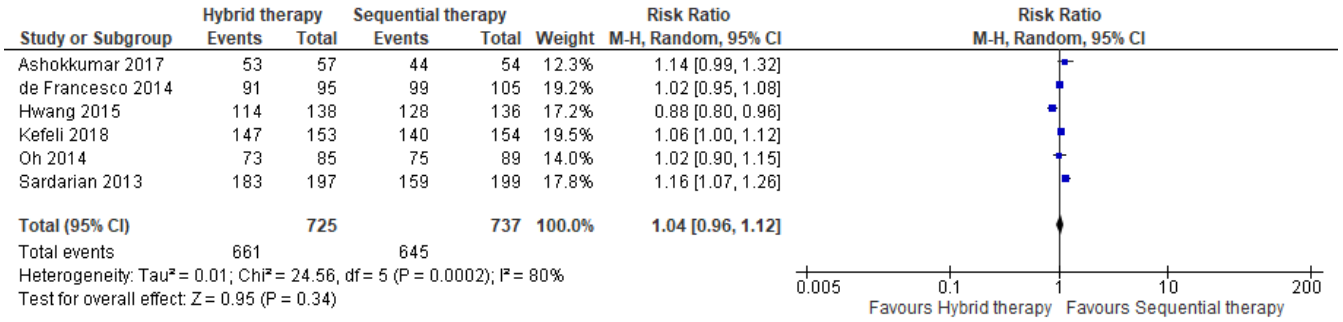

Figure 10: Forest plot comparing eradication rates of Hybrid therapy and Sequential therapy (per-protocol analysis) in the treatment of *Helicobacter pylori*.

As far as adverse events are concerned, HT revealed a 10% increase in tendency for adverse events in comparison to ST, but no statistically significant difference was found (RR 1.10 [0.89, 1.36], p = 0.39, I^2 = 35%) (Figure 11).

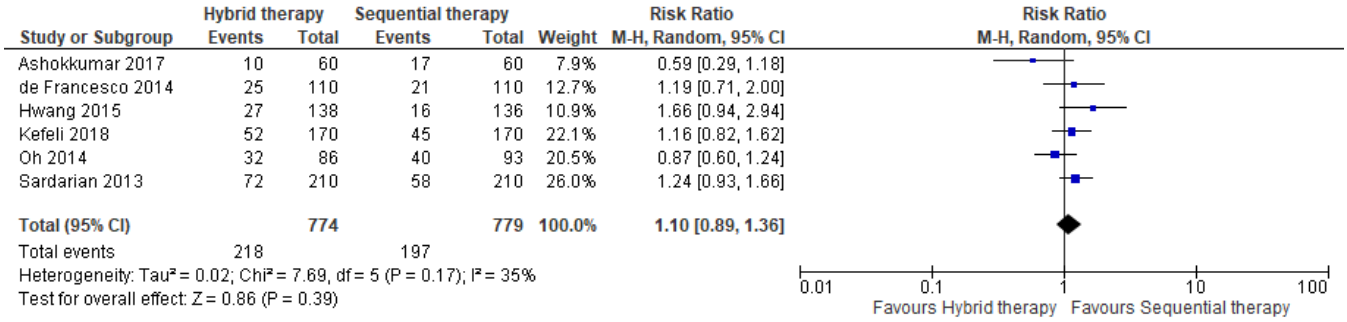

Figure 11: Forest plot comparing adverse events of Hybrid therapy and Sequential therapy in the treatment of *Helicobacter pylori*.

The compliance rates were not statistically different between the groups (RR 1 [0.98, 1.01], p = 0.46, I^2 = 0%) (Figure 12).

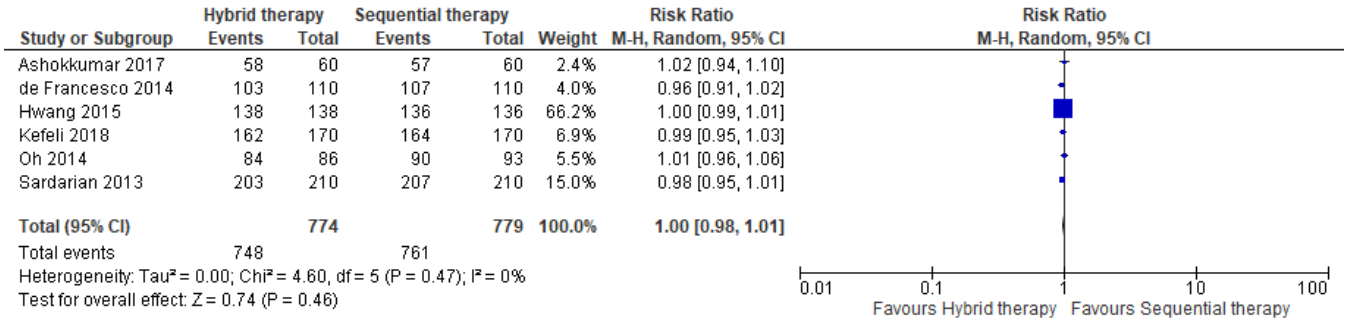

Figure 12: Forest plot comparing compliance rates of Hybrid therapy of Sequential therapy in the treatment of *Helicobacter pylori*.

DISCUSSION

HT is a non-bismuth quadruple therapy. It was first proposed and reported by Hsu et al, and demonstrated excellent eradication rates, as well as a relevant compliance and safety profile (9). In subsequent years, this alternative therapy has been recommended as first line therapy in populations naïve to macrolide including therapies and resistant to either clarithromycin or metronidazole are high (35). This may be particularly relevant in the central region of Portugal, where resistance rates to clarithromycin or metronidazole are high (16). Another advantage of this treatment regimen over CT is the shorter duration of exposure to metronidazole and clarithromycin, theoretically leading to a reduction in side effects to these antibiotics.

This systematic review and meta-analysis included 10 studies that compare HT with either ST or CT in a population of 2993 patients. To the best of our knowledge, this is one of the largest populations in whom efficacy of HT was assessed with a meta-analysis to this date.

In our study, HT demonstrated similar eradication rates compared to sequential and concomitant therapies.

Among the included studies, HT achieved on average an eradication rate of 86%, which is superior to the recommended eradication rate of 80% in ITT analysis proposed by the Maastricht I Consensus report (36). This finding reinforces the power of this regimen to eradicate Hp proposed by previous studies (7).

Of the 10 included studies, two of them showed that HT was superior to ST (31,34); 6 studies showed similar eradication rates when comparing hybrid to concomitant and/or sequential groups in high antibiotic resistant regions (21,27–30,33); only two studies demonstrated that HT was inferior to ST, a phenomenon that may be attributed to high levels of antibiotic resistance in those countries (22,32). When comparing adverse events between HT and CT, the initial analysis was not statistically significant. Due to the high heterogeneity of the groups, we omitted the Cuadrado-Lavin et al study (27) and the heterogeneity became zero. With this fixed analysis, we verified that HT had 17% lower risk of adverse effects occurrence when compared to CT. We believe that the heterogeneity can be attributed a significantly higher occurrence of adverse events in HT group. HT and ST did not show statistically significant differences in the adverse events outcome. Regarding compliance rates, HT illustrated higher tendency for lower adherence to this regimen compared to ST, but it was not statistically significant. In the same groups, there was no difference in the compliance rates.

The evidence presented in this review is conflicting with the results outlined in a previous review comparing HT with other non-bismuth therapies (19). Hsu et al demonstrated that HT was more effective than ST, but similar in efficacy when compared to CT. The authors attribute these results to the differences in antibiotic resistance in the populations studied, as well as to

the high heterogeneity among individual characteristics of the patients included (9). In fact, future challenges regarding this matter include the assessment of differences in eradication rates having regional antibiotic resistance patterns in consideration.

Nevertheless, we acknowledge some limitations of this review. Although initially contemplated in the design of the study, we were not able to perform meta-analysis comparing hybrid therapy to standard triple therapy, because only one trial with standard triple therapy completed the criteria to be included in our final pool of studies (27). We consider this comparison would be relevant to reinforce the loss of efficacy of standard triple therapy. However, triple therapy has already shown a decrease in eradication rates to unacceptable levels (37). As a matter of fact, a recent report showed a lesser tendency in triple therapy prescription in many European countries (38). Moreover, antibiotic resistance and its effects on eradication rates was not compared because only one of the included studies reported this outcome (30). In addition, no comparison between durations of HT was performed. Another possible limitation of the review is the fact that the included RCTs were not blinded to the treatment regimens attributed to the groups, placing the studies at high risk for performance and detection biases (Figure 2). We attribute the lack of blinding of the studies to the complexity of the regimens being administered. Therefore, we do not believe that these biases compromise the quality of the included RCTs.

Our meta-analysis has some key strengths, such as the inclusion of only randomized controlled trials and the low heterogeneity between studies, which powers our statistical analysis. In fact, to the best of our knowledge, this meta-analysis is the most recent, complete, and accurate, with a good level of evidence, comparing HT and other commonly used quadruple regimens. Our work represents a step further in the comprehension of the efficacy of HT in the treatment of Hp.

CONCLUSION

In conclusion, we demonstrated that hybrid therapy has similar eradication rates to sequential and concomitant regimens. Hybrid therapy also showed significantly less adverse events when compared to concomitant therapy and no significant difference when compared to sequential therapy. Moreover, it revealed that hybrid therapy had a slightly higher compliance rates when compared to concomitant rates.

Overall, we conclude that hybrid therapy is a favourable option as first-line eradication of *Helicobacter pylori* which may have encouraging clinical benefits in our country.

FUNDING

None.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

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BIBLIOGRAPHIC REFERENCES

1. Hunt RH, Xiao SD, Megraud F, Leon-Barua R, Bazzoli F, van der Merwe S, et al. World gastroenterology organisation global guideline: Helicobacter pylori in developing countries. Journal of Clinical Gastroenterology. 2011 May;45(5):383–8.

2. Hu Y, Zhu Y, Lu NH, Shi Q. Recent progress in Helicobacter pylori treatment. Vol. 133, Chinese Medical Journal. Lippincott Williams and Wilkins; 2020. p. 335–43.

3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer. 2015 Mar 1;136(5): E359–86.

4. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Vol. 112, American Journal of Gastroenterology. Nature Publishing Group; 2017. p. 212–38.

5. Leung WK, Wong IOL, Cheung KS, Yeung KF, Chan EW, Wong AYS, et al. Effects of Helicobacter pylori Treatment on Incidence of Gastric Cancer in Older Individuals. Gastroenterology. 2018 Jul 1;155(1):67–75.

6. Choi IJ, Kook M-C, Kim Y-I, Cho S-J, Lee JY, Kim CG, et al. Helicobacter pylori Therapy for the Prevention of Metachronous Gastric Cancer. New England Journal of Medicine. 2018 Mar 22;378(12):1085–95.

7. Bagirova M, Allahverdiyev AM, Abamor ES, Aliyeva H, Unal G, Tanalp TD. An overview of challenges to eradication of H. pylori infection and future prospects.

8. Song ZQ, Liu J, Zhou LY. Hybrid therapy regimen for Helicobacter pylori eradication. Vol. 129, Chinese Medical Journal. Chinese Medical Association; 2016. p. 992–9.

9. Song Z, Zhou L, Zhang J, He L, Bai P, Xue Y. Hybrid Therapy as First-Line Regimen for Helicobacter pylori Eradication in Populations with High Antibiotic Resistance Rates. Helicobacter. 2016 Oct 1;21(5):382–8.

10. Flores-Treviño S, Mendoza-Olazarán S, Bocanegra-Ibarias P, Maldonado-Garza HJ, Garza-González E. Helicobacter pylori drug resistance: therapy changes and challenges. Vol. 12, Expert Review of Gastroenterology and Hepatology. Taylor and Francis Ltd; 2018. p. 819–27.

11. Megraud F, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, et al. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. Gut. 2013 Jan 1;62(1):34–42.

12. Gumurdulu Y, Serin E, Özer B, Kayaselcuk F, Ozsahin K, Mansur Cosar A, et al. Low eradication rate of Helicobacter pylori with triple 7-14 days and quadriple therapy in Turkey. World Journal of Gastroenterology Turkey World J Gastroenterol [Internet]. 2345;10(5):668–71. Available from: http://www.wjgnet.com/1007-9327/10/668.asp

13. de Francesco V, Margiotta M, Zullo A, Hassan C, Giorgio F, Burattini O, et al. Prevalence of primary clarithromycin resistance in Helicobacter pylori strains over a 15 year period in Italy. Journal of Antimicrobial Chemotherapy. 2007 Apr;59(4):783–5.

14. Almeida N, Donato MM, Romãozinho JM, Luxo C, Cardoso O, Cipriano MA, et al. Beyond Maastricht IV: Are standard empiric triple therapies for helicobacter pylori still seful in a South-European country? BMC Gastroenterology. 2015 Feb 15;15(1).

15. Savoldi A, Carrara E, Graham DY, Conti M, Tacconelli E. Prevalence of Antibiotic Resistance in Helicobacter pylori: A Systematic Review and Meta-analysis in World Health Organization Regions. Gastroenterology. 2018 Nov 1;155(5):1372-1382.e17.

16. Almeida N, Romãozinho JM, Donato MM, Luxo C, Cardoso O, Cipriano MA, et al. Helicobacter pylori antimicrobial resistance rates in the central region of Portugal. Clinical Microbiology and Infection. 2014 Nov 1;20(11):1127–33.

17. Lopo I, Libânio D, Pita I, Dinis-Ribeiro M, Pimentel-Nunes P. Helicobacter pylori antibiotic resistance in Portugal: Systematic review and meta-analysis. Vol. 23, Helicobacter. Blackwell Publishing Ltd; 2018.

18. Hsu PI, Wu DC, Wu JY, Graham DY. Modified Sequential Helicobacter pylori Therapy: Proton Pump Inhibitor and Amoxicillin for 14Days with Clarithromycin and Metronidazole added as a Quadruple (Hybrid) Therapy for the Final 7Days. Helicobacter. 2011 Apr;16(2):139–45.

19. Hsu PI, Lin PC, Graham DY. Hybrid therapy for Helicobacter pylori infection: A systemic review and meta-analysis. Vol. 21, World Journal of Gastroenterology. WJG Press; 2015. p. 12954–62.

20. Chen KY, Lin TJ, Lin CL, Lee HC, Wang CK, Wu DC. Hybrid vs sequential therapy for eradication of Helicobacter pylori in Taiwan: A prospective randomized trial. World Journal of Gastroenterology. 2015 Sep 28;21(36):10435–42.

21. de Francesco V, Hassan C, Ridola L, Giorgio F, Ierardi E, Zullo A. Sequential, concomitant and hybrid first-line therapies for Helicobacter pylori eradication: A prospective randomized study. Journal of Medical Microbiology. 2014;63(PART 5):748–52.

22. Oh DH, Lee DH, Kang KK, Park YS, Shin CM, Kim N, et al. The efficacy of hybrid therapy as first-line regimen for Helicobacter pylori infection compared with sequential therapy. Journal of Gastroenterology and Hepatology (Australia). 2014;29(6):1171–6.

23. Zullo A, Scaccianoce G, de Francesco V, Ruggiero V, D'Ambrosio P, Castorani L, et al. Concomitant, sequential, and hybrid therapy for H.pylori eradication: A pilot study. Clinics and Research in Hepatology and Gastroenterology. 2013 Dec;37(6):647–50.

24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Revista Espanola de Nutricion Humana y Dietetica. 2016;20(2):148–60.

25. Graham DY. Efficient Identification and Evaluation of Effective Helicobacter pylori Therapies. Clinical Gastroenterology and Hepatology. 2009 Feb;7(2):145–8.

26. CASP_RCT_Checklist_PDF_Fillable_Form.

27. Cuadrado-Lavín A, Salcines-Caviedes JR, Diaz-Perez A, Carrascosa MF, Ochagavía M, Fernandez-Forcelledo JL, et al. First-line eradication rates comparing two shortened non-bismuth quadruple regimens against Helicobacter pylori: An open-label, randomized, multicentre clinical trial. Journal of Antimicrobial Chemotherapy. 2015 Aug 1;70(8):2376–81.

28. Heo J, Jeon SW, Jung JT, Kwon JG, Lee DW, Kim HS, et al. Concomitant and hybrid therapy for Helicobacter pylori infection: A randomized clinical trial. Journal of Gastroenterology and Hepatology (Australia). 2015 Sep 1;30(9):1361–6.

29. Mestrovic A, Perkovic N, Bozic J, Ivelja MP, Vukovic J, Kardum G, et al. Randomised clinical trial comparing concomitant and hybrid therapy for eradication of Helicobacter pylori infection. PLoS ONE. 2020 Dec 1;15(12 December).

30. Molina-Infante J, Romano M, Fernandez-Bermejo M, Federico A, Gravina AG, Pozzati L, et al. Optimized nonbismuth quadruple therapies cure most patients with Helicobacter pylori infection in populations with high rates of antibiotic resistance. Gastroenterology. 2013;145(1).

31. Ashokkumar S, Agrawal S, Mandal J, Sureshkumar S, Sreenath GS, Kate V. Hybrid therapy versus sequential therapy for eradication of Helicobacter pylori: A randomized controlled trial. Journal of Pharmacology and Pharmacotherapeutics. 2017 Apr 1;8(2):62–7.

32. Hwang JJ, Lee DH, Yoon H, Shin CM, Park YS, Kim N. Efficacy of moxifloxacin-based sequential and hybrid therapy for first-line Helicobacter pylori eradication. World Journal of Gastroenterology. 2015 Sep 21;21(35):10234–41.

33. Kefeli A, Başyigit S, Yeniova AO, Ozkan S, Nazligul Y. Comparison of the efficacy and safety of hybrid and sequential therapies as a first-line regimen for Helicobacter pylori infection in Turkey. Archives of Medical Science. 2018 Mar 1;14(2):276–80.

34. Sardarian H, Fakheri H, Hosseini V, Taghvaei T, Maleki I, Mokhtare M. Comparison of hybrid and sequential therapies for helicobacter pylori eradication in iran: A prospective randomized trial. Helicobacter. 2013 Apr;18(2):129–34.

35. Kim SY, Chung JW. Best helicobacter pylori eradication strategy in the era of antibiotic resistance. Antibiotics. 2020 Aug 1;9(8):1–16.

36. Leading article Current European concepts in the management of Helicobacterpylori infection. The Maastricht Consensus Report.

37. Liou JM, Chen CC, Chen MJ, Chen CC, Chang CY, Fang YJ, et al. Sequential versus triple therapy for the first-line treatment of Helicobacter pylori: A multicentre, open-label, randomised trial. The Lancet. 2013;381(9862):205–13.

38. Nyssen OP, Bordin D, Tepes B, Pérez-Aisa Á, Vaira D, Caldas M, et al. European Registry on Helicobacter pylori management (Hp-EuReg): Patterns and trends in first-line empirical eradication prescription and outcomes of 5 years and 21 533 patients. Gut. 2021 Jan 1;70(1):40–54.