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**THE EFFECTIVITY OF TRIPLE THERAPY COMPOSITION ON DYSPEPSIA WITH  
*HELICOBACTER PYLORI* INFECTION: A SYSTEMATIC REVIEW****T P Simanjaya<sup>1</sup>, E Harfiani<sup>2</sup>, M Citrawati<sup>3</sup>**<sup>1</sup>Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, Jakarta Selatan, Jakarta, Indonesia<sup>2</sup>Department of Pharmacology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, Jakarta Selatan, Jakarta, Indonesia<sup>3</sup>Department of Physiology, Faculty of Medicine, Universitas Pembangunan Nasional Veteran Jakarta, Jakarta Selatan, Jakarta, Indonesia\*Correspondence: theodoraputris@upnvj.ac.id

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**ABSTRACT**

Dyspepsia is a disease with one or more symptoms relating to abnormalities in gastroduodenal. One of the factors that influence dyspepsia is *Helicobacter pylori* (*H. pylori*). Clarithromycin-based triple therapy is recommended as first line eradication treatment. Resistance towards clarithromycin is increasing and causing eradication rates in Clarithromycin-based triple therapy to decrease. The purpose of this study was to determine the effectiveness of triple therapy variation on dyspepsia with *H. pylori* infection. Data was collected through literature searches on two different databases using the preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2020. This systematic review included all relevant articles from 2011-2021. Six studies met the inclusion criteria. The results showed that metronidazole-based triple therapy is effective in eradicating *H. pylori* due to its eradication rate surpassing the target rate of 80%. The highest eradication rates in intention-to-treat (ITT) and per-protocol (PP) were 94.3% and 93.5%, respectively. The best triple therapy composition is metronidazole-based triple therapy with 7 days of duration.

**Keywords:** Clarithromycin, Dyspepsia, *Helicobacter pylori*, Triple Therapy*Received: April 2022,**Accepted: June 2022,**Published: June 2022*

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**INTRODUCTION**

Dyspepsia is a disease with one or more symptoms associated with gastroduodenal abnormalities (Simadibrata et al., 2014). Symptoms may include nausea, epigastric pain, a burning sensation in the epigastrium, or early satiety which is sometimes described as discomfort after eating (Talley & Cook, 2019). The pathophysiology of dyspepsia still cannot be explained, but one of the factors that influence the symptoms of dyspepsia is *Helicobacter pylori* (*H. pylori*) infection (Simadibrata et al., 2014).

The prevalence of *H. pylori* infection is in the range between 10-20% of all infections related to gastroduodenal complaints. The

prevalence of *H. pylori* infection in patients with functional dyspepsia ranges from 20-40% (Pramono & Syam, 2014). 90% of patients with duodenal ulcers and 50-80% of patients with gastric ulcers have *H. pylori* infection (Carroll et al., 2016).

The results of endoscopy conducted from January 2003 to April 2004 at several centers in Indonesia on 550 dyspeptic patients, found 44.7% of cases with minimal abnormalities in gastritis and duodenitis. There were 6.5% cases with gastric ulcer and 8.2% normal cases. Data on the prevalence of *H. pylori* infection in peptic ulcer patients without a history of taking non-steroidal anti-inflammatory drugs varies from 90%-100%

and for functional dyspepsia patients as much as 20-40% with various diagnostic methods such as serology, culture, and histopathology. The prevalence of *H. pylori* infection in dyspeptic patients was found to be quite high in Makassar in 2011 (55%), in Solo in 2008 (51.8%), in DI Yogyakarta (30.6%) and in Surabaya in 2013 (23,5%) (Simadibrata et al., 2014).

The recommended first-line treatment for dyspepsia with *H. pylori* infection according to the National Consensus on the Management of Dyspepsia and *Helicobacter pylori* infection is Triple Therapy consisting of PPIs, and antibiotics, namely Amoxicillin and Clarithromycin. The results of the meta-analysis conducted by Ben Wang et al (2014) reported that Standard Triple Therapy in China was no more effective than Quadruple Therapy or Sequential Therapy. This is influenced by the resistance of several bacterial strains to Clarithromycin. There are several compositions used in Triple Therapy in the management of dyspepsia caused by *H. pylori*. Therefore, this study was conducted to see the effectiveness of using Clarithromycin compared to other antibiotics in Triple Therapy.

## MATERIALS AND METHODS

This research was a literature review with a systematic review method. This research design is a method that identifies, assesses, and synthesizes all related research on a particular topic. Systematic reviews use detailed and comprehensive plans and search strategies based on presuppositions with the aim of reducing bias (Uman, 2011). This systematic review study method was carried out using the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2020 method which was formed to help researchers report transparently why a review was conducted, what the authors did, and what the authors found (Page et al., 2021).

This research was conducted from December 2021 to January 2022. The population of this research is all research articles published in PubMed and Google

Scholar. The article search was conducted in December 2021. The PICO (Population, Intervention, Comparison and Outcome) method is a good method to facilitate the search for related scientific literature. The search was carried out in the PubMed and Google Scholar data centers using keywords such as, *Helicobacter pylori*, Clarithromycin, Amoxicillin, Metronidazole, Azithromycin, and Furazolidone. Articles that meet the criteria were reviewed and extracted. Search results were documented within the Mendeley application for compiling references.

The research studies obtained by the next researcher will be tested for quality using Critical Appraisal tools which refers to the study instrument made by The Joanna Briggs Institute (JBI) for the study Randomized Controlled Trials namely the JBI Critical Appraisal Checklist for Randomized Controlled Trials. The article quality assessment aims to assess the methodological quality of a study and to determine the extent to which a study conveys possible bias in design, implementation, and analysis. This study instrument consists of 13 questions that can be answered with “yes”, “no”, “not clear” or “not applicable”.

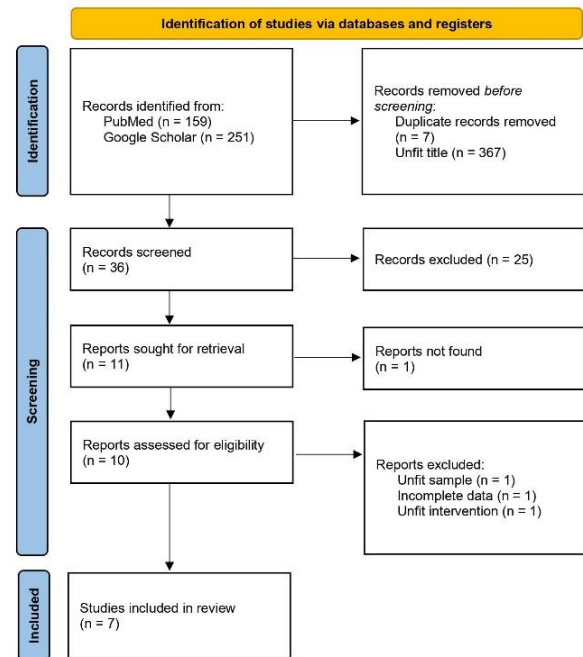
Researchers extracted data which were grouped into methods, participants, and interventions. The method group consists of the name of the first author, year of publication, country of origin of the study, and number of study centers. The group of participants consisted of the number of participants, the average age, gender, diagnostic investigations, and a diagnosis of dyspepsia. The intervention group consisted of the therapy used (name of drug, dose, and duration), and the main therapy substitute (name of drug, dose, and duration). Synthesis of data in this systematic review focused on variations in triple therapy regimens other than a combination of Proton Pump Inhibitor (PPI), Amoxicillin and Clarithromycin compared to Triple Therapy using a Clarithromycin substitute. The eradication effectiveness of *H. pylori* was determined by

measuring the eradication rates by intention-to-treat (ITT) and per-protocol (PP) which was carried out in a narrative manner by grouping data from similar extractions according to the results to be measured. Researchers collect the data using Microsoft Office Excel 2010. The data that has been collected will be discussed to draw conclusions.

## RESULT

Researcher used two online databases as data sources, namely PubMed and Google Scholar with the following keywords,

- *Helicobacter pylori* AND Clarithromycin AND Amoxicillin
- *Helicobacter pylori*[MeSH] AND Clarithromycin[MeSH] AND Amoxicillin [MeSH] AND Metronidazole[MeSH]
- *Helicobacter pylori*[MeSH] AND Clarithromycin[MeSH] AND Amoxicillin [MeSH] AND Azithromycin[MeSH]
- *Helicobacter pylori*[MeSH] AND Clarithromycin[MeSH] AND Amoxicillin [MeSH] AND Furazolidone[MeSH]
- RCT AND amoxicillin AND clarithromycin AND proton pump inhibitor OR omeprazole OR metronidazole OR azithromycin "triple therapy" -acupuncture - "systematic review" -"meta-analysis"



**Figure 1.** PRISMA Flow Chart

The author has identified articles that will be discussed in the form of a systematic review based on previously defined keywords and literature strategies. There were 410 articles identified as randomized controlled trials in the last 10 years. There were 159 articles found from the PubMed data center and 251 articles found from the Google Scholar data center. The author then filters the articles found by removing articles with inappropriate titles and duplicated articles. There are 7 duplicate articles and 367 articles with inappropriate titles. The author continues filtering with 36 recorded articles. A total of 25 articles with inappropriate abstracts were excluded by the author and 1 article could not be found. The author selected at the feasibility stage for 10 articles. Found 1 article with an inappropriate sample, 1 article with incomplete data, and 1 article with an inappropriate intervention. The author only found 7 articles that matched the inclusion criteria and could be reviewed in this systematic review.

The quality of the studies on the articles that have been screened will be assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Randomized Controlled Trials. Through this assessment, an article can be said to have good quality if the score exceeds 80% while a score between

50-80% indicates the article has moderate quality. If the score is below 50%, then the article has poor quality. In this systematic review, 7 articles were assessed using 13 questions from the JBI Critical Appraisal Checklist for Randomized Controlled Trials. The articles that will be reviewed by the author are journals with good and moderate quality (Table 1).

**Table 1.** Literature Quality Assessment

Literature	Results (%)	Category
(Adachi et al., 2017)	61.53%	Moderate
(Gungor et al., 2015)	53.84%	Moderate
(Hajaghahammadi et al., 2014)	53.84%	Moderate
(Khoshnood et al., 2014)	61.53%	Moderate
(Loghmani et al., 2012)	46.15%	Poor
(Nishizawa et al., 2015)	84.61%	Good
(Sarkeshikian, Iranikhah and Ghadir, 2013)	53.84%	Moderate

All search results consist of 3 articles from Iran, 1 article from Turkey, and 2 articles from Japan. The mean age of the oldest sample is 63.86 from Adachi et al. (2017) and the mean age of the youngest sample is 36.24 from Sarkeshikian, Iranikhah and Ghadir (2013). Dyspepsia diagnoses included in these studies include peptic ulcer disease (PUD), gastric erosion, duodenal erosion, non-ulcer dyspepsia (NUD), dyspeptic symptoms, atrophic gastritis and upper gastrointestinal

symptoms which are included in dyspepsia. The diagnostic methods carried out in the 6 studies in the table consist of rapid urease test (RUT), urease breath test (UBT), endoscopy, biopsy, stool antigen test, histopathology, culture, and *H. Pylori* antibody serum test with the most used diagnostic methods in the form of RUT and UBT.

The results of data synthesis showed eradication rate intention-to-treat (ITT) data from 6 studies. The results of the comparison of 6 studies have the lowest ITT eradication rate of 42% with triple therapy based on Clarithromycin obtained from the study of Gungor et al. (2015). The highest ITT eradication rate value was 94.3% with Metronidazole-based triple therapy obtained from the study of Adachi et al. (2017). These data show the eradication rate per protocol (PP) data from 6 studies. The results of the comparison of 6 studies have the lowest PP eradication rate of 48.3% with triple therapy based on Clarithromycin obtained from the study of Gungor et al. (2015). The highest PP eradication rate value is 93.5% with Metronidazole-based triple therapy obtained from the study of Nishizawa et al. (2017) (Table 3).

**Table 2.** Data Extraction

Studies	(Sarkeshikian et al., 2013)	(Hajaghahammadi et al., 2014)	(Khoshnood et al., 2014)	(Gungor et al., 2015)	(Nishizawa et al., 2015)	(Adachi et al., 2017)
Year	2013	2014	2014	2015	2015	2017
Country of origin	Iran	Iran	Iran	Turkey	Japan	Japan
Number of Study Centers	1	1	2	NA	16	1
Number of Patients (Clarithromycin/substitute)	165 (76/89)	120 (59/61)	70 (35/35)	200 (100/100)	124 (60/64)	140 (68/72)
Age (mean)	36.24	41.42	41.53	43	60.77	63.86
Gender (M/F)	(100/65)	(50/70)	NA	(84/116)	(51/73)	(68/72)
Dyspepsia Diagnosis	PUD, gastric/duodenal erosion	PUD, NUD	duodenal/gastric ulcer	dyspeptic symptoms	atrophic gastritis	PUD, chronic gastritis, UGS
Diagnosis Method	Pre: RUT Post: UBT (6 weeks later)	Pre: RUT	Pre: RUT Post: endoscopy	Pre: UBT, stool antigen test, RUT, or	Pre and Post: UBT	Pre: RUT, culture,

		Post: UBT (2 weeks later)	, biopsy (2 months later)	histopatholo gy Post: UBT (6 weeks later)	(12 weeks later)	<i>H.pylori</i> antibody serum test, or stool test Post: UBT (4 weeks later)
<i>Triple Therapy Clarithrom ycin-based (Duration)</i>	O(2x 20 mg) A(2x1000mg) C(2x 500mg) (10 days)	O(2x 20 mg) A(2x 500mg) C(2x 500mg) (14 days)	O(2x 20 mg) A(2x1000mg) C(2x 500mg) (14 days)	P(2x 40 mg) A(2x1000mg) C(2x 500mg) (14 days)	R(2x 10 mg) A(2x 750mg) C(2x 400mg) (7 days)	E(2x 20 mg) A(2x 750mg) C(2x 400mg) (7 days)
<i>Triple Therapy Non- Clarithrom ycin-based (Duration)</i>	O(2x 20 mg) A(2x1000mg) Az(2x 250mg the first 4 days) (250 mg the next 6 days) (10 days)	O(2x 20 mg) A(2x 500mg) F(2x 100mg) (14 days)	O(2x 20 mg) A(2x1000mg) ) Az(250mg) (10 days)	P(2x 40 mg) A(2x1000mg) M(2x 500mg) (14 days)	R(2x 10 mg) A(2x 750mg) M(2x 250mg) (7 days)	E(2x 20 mg) A(2x 750mg) M(2x 500mg) (7 days)

C: Clarithromycin; M: Metronidazole; F: Furazolidone; A: Amoxicillin; O: Omeprazole; P: Pantoprazole; E: Esomeprazole; R: Rabeprazole; PUD: Peptic Ulcer Disease; NUD: Non-Ulcer Disease; USG: Upper gastrointestinal Symptoms; Pre: method of diagnosis before the study; Post: method of diagnosis after therapy; RUT: Rapid Urease Test; UBT: Urease Breath Test

**Table 3.** Data Synthesis

No	Studies	% Eradication Rate (Triple therapy based on Clarithromycin) (ITT/PP)	% Eradication Rate (Triple therapy based on Metronidazole) (ITT/PP)	% Eradication Rate (Triple therapy based on Azithromycin) (ITT/PP)	% Eradication Rate (Triple therapy based on Furazolidon e) (ITT/PP)
1.	Adachi et al. (2017)	72.7/70.6	94.3/91.7	-	-
2.	Gungor et al. (2015)	42/48.3	52/54.2	-	-
3.	Nishizawa et al. (2015)	73.3/77.2	90.6/93.5	-	-
4.	Khoshnood et al. (2014)	84.6/82.9	-	79.5/77.1	-
5.	Sarkeshikian, Iranikhah and Ghadir (2013)	82.9/82.9	-	75.3/75.3	-
6.	Hajaghamohammadi et al. (2014)	57.6/57.6	-	-	78.8/78.8

**DISCUSSION**

Eradication of *H. pylori* is important because *H. pylori* infection is an important risk factor for peptic ulcers, chronic gastritis, maltoma and gastric adenocarcinoma (Khoshnood et al., 2014). This eradication is also the most effective approach to the prevention of gastric cancer, this treatment

can prevent the metachronous development of gastric cancer in patients already undergoing endoscopic treatment for gastric cancer, severe gastric atrophy and/or intestinal metaplasia (Adachi et al., 2017). Eradication of *H. pylori* plays a role in preventing and treating these diseases. Some of the factors considered in the treatment

regimen are the cost of treatment, effectiveness, side effects and duration of treatment needed (Khoshnood et al., 2014).

The triple therapy regimen based on Clarithromycin in this study has various eradication rates, there are values that pass the eradication rate target of 80%. This indicates that Clarithromycin-based triple therapy is still effective in eradicating *H. pylori*. The factor that plays a major role in determining the success of *H. pylori* eradication is the presence of a population that is resistant to Clarithromycin. The research of Khoshnood et al. (2014) and Sarkeshian, Iranikhah and Ghadir (2013) have an eradication rate of target value indicating that Clarithromycin-based triple therapy is effective in eradicating *H. pylori*. This is in line with research conducted by Prasertpetmanee, Mahachai and Vilaichone (2013). The study found the eradication rate with the Clarithromycin-based triple therapy regimen was 100% for the 14-day duration regimen and 92.7% for the 7-day duration regimen. This study also found that there was resistance to Metronidazole by 40% while no resistance to Clarithromycin was found, indicating that the sample population used in the study by Prasertpetmanee, Mahachai and Vilaichone (2013) was not resistant to Clarithromycin so that its effectiveness could exceed the target (Prasertpetmanee et al., 2013).

Opinions regarding the duration of Clarithromycin-based triple therapy regimens vary widely among available studies. Research Onyekwere (2014) and Kim et al. (2020) found that there was no more effective duration between 7 days and 10 days of Clarithromycin-based triple therapy (Kim et al., 2020; Onyekwere, 2014). In contrast to the research conducted by Leow et al. (2018), Choi (2012), and Wang et al. (2015). These studies found that a 14-day Clarithromycin-based triple therapy regimen was more effective than a 7-day or 10-day regimen (Choi, 2012; Leow et al., 2018; Wang et al., 2015).

The incidence of side effects of Clarithromycin-based triple therapy

regimens in the studies in this study ranged from 0-25.5%. The lowest incidence of side effects at 0% was obtained from Hajaghamohammadi et al. (2014) and the highest incidence of side effects, namely 25.5%, was obtained from Khoshnood et al. (2014). Drug side effects reported in a study conducted by Gungor et al. (2015), Nishizawa et al. (2015), and Sarkeshian, Iranikhah and Ghadir (2013) include nausea or vomiting, diarrhea, abdominal discomfort, impaired sense of taste, skin rashes, and headaches.

Comparison of variations in triple therapy regimens based on Clarithromycin replacement shows that Metronidazole-based triple therapy regimens have a higher eradication rate, both intention-to-treat (ITT) and per-protocol (PP). This result is in line with the research conducted by Li et al. (2020). The study found that Metronidazole-based triple therapy regimens had better efficacy in recent years, especially for patients over 60 years of age (Li et al., 2020). The lower eradication rate in the Clarithromycin-based triple therapy regimen may be due to drug resistance. *H. pylori* mutations complicate target recognition by the drug Clarithromycin (Marques et al., 2020).

The study population is the main factor associated with drug resistance. In the research of Adachi et al. (2017), the results of the study support the effectiveness of Metronidazole-based triple therapy because the percentage of Clarithromycin resistance in the Japanese population reaches 39.3%, while Metronidazole resistance is only 3.67%. This difference in resistance helps research in the form of significantly different eradication rate values. Adachi et al. (2017) also provided a study with a specific sample where patients had resistance to Clarithromycin and the eradication rate results between Clarithromycin-based triple therapy and Metronidazole-based triple therapy were significantly different (51.9% and 95.7%) (Adachi et al., 2017).

In the research of Gungor et al. (2015), the eradication rate of triple therapy based on

Clarithromycin and Metronidazole is low. This study is in line with the research of Loghmari et al. (2012). Research Loghmari et al. (2012) found Metronidazole-based triple therapy regimens were no more effective than Clarithromycin-based triple therapy (Loghmari et al., 2012). In the research sample Loghmari et al. (2012) involving the Tunisian population, there are resistance to Metronidazole so that it affects the eradication rate of triple therapy based on Metronidazole. Research by Gungor et al. (2015) is also influenced by population, specifically the population of the country of Turkey. Resistance to the drug Clarithromycin in the Turkish population is 41.9% and according to another study, this resistance rate reaches 48.2%. Resistance to the drug Metronidazole in the Turkish population also reached an equivalent figure of 41.9%. Research conducted by Gungor et al. (2015) did not examine and record data on drug resistance in patients but the overall percentage in the Turkish population above can indirectly affect the eradication rate of triple therapy based on Clarithromycin and Metronidazole in the study of Gungor et al. (2015) based on information regarding the Turkish population (Gungor et al., 2015).

The advantages of using Metronidazole-based triple therapy are not only limited to the eradication rate which is higher than Clarithromycin-based triple therapy. In terms of treatment costs, the use of Metronidazole is also cheaper. Clarithromycin costs up to 5 times that of Metronidazole. In the eradication of *H. pylori* based on triple therapy for 7 days, treatment costs will be cheaper if using triple therapy based on Metronidazole compared to triple therapy based on Clarithromycin. With a more affordable treatment cost, Metronidazole-based triple therapy has a high eradication rate and can prevent failure in *H. pylori* eradication therapy (Nishizawa et al., 2015).

The incidence of side effects of Metronidazole-based triple therapy regimens in studies in this study ranged from 8.3-17.5%. The lowest incidence of side effects

is 8.3% obtained from research by Gungor et al. (2015) and the highest incidence of side effects, namely 17.5%, was obtained from the research of Nishizawa et al. (2017). Drug side effects reported in a study conducted by Gungor et al. (2015), and Nishizawa et al. (2015) include nausea or vomiting, diarrhea, abdominal discomfort, impaired sense of taste, skin rashes, liver dysfunction and headaches.

Azithromycin is considered as an antimicrobial in a variety of triple therapy regimens other than Clarithromycin and Metronidazole because of its acid-resistant properties, longer half-life, and higher concentrations on the gastric surface after oral administration of the drug (Khoshnood et al., 2014). Azithromycin has a mean inhibitory and very good bactericidal concentration for *H. pylori*, namely 0.25 mg/L and 0.5 mg/L, respectively. After oral ingestion, the drug is concentrated on the gastric surface and the half-life of Azithromycin is long, counting for several days (Sarkeshikian et al., 2013).

Comparison of variations of Clarithromycin-based triple therapy regimens and their substitutes shows that Azithromycin-based triple therapy regimens have a lower eradication rate than Clarithromycin-based triple therapy regimens. This result is in line with the research conducted by Cammarota et al. (1996) and Silva et al. (2008) (Cammarota et al., 1996; Silva et al., 2008). Research conducted by Cammarota et al. (1996) and Silva et al. (2008) found that Azithromycin-based triple therapy has a low eradication rate. Azithromycin is considered as a substitute for Clarithromycin in triple therapy regimens based on affordable drug prices and high drug adherence, but the efficacy of Azithromycin-based triple therapy regimens in eradicating *H. pylori* is low (Silva et al., 2008). Its efficacy in *H. pylori* eradication may decrease further in the future. This can happen because Azithromycin is widely used as sole therapy for respiratory tract infections which may

increase Azithromycin-resistant mutations (Sarkeshikian et al., 2013).

The incidence of side effects of Azithromycin-based triple therapy regimens in studies in this study ranged from 16.8-31.4%. The lowest incidence of side effects, namely 16.8%, was obtained from the study of Sarkeshikian, Iranikhah and Ghadir (2013) and the highest incidence of side effects, which was 31.4%, was obtained from the study of Khoshnood et al. (2014). Drug side effects reported by the study of Sarkeshikian, Iranikhah and Ghadir (2013) include diarrhea, bitter tongue, headache, and skin rash.

The results of the comparison of variations in the triple therapy regimen based on Furazolidone show that the triple therapy regimen has an eradication rate value of 78.8% in ITT and PP obtained from the research of Hajaghamohammadi et al. (2014). Comparison of variations in the triple therapy regimen based on Clarithromycin and its substitutes shows that the triple therapy regimen based on Furazolidone has a higher eradication rate value than the triple therapy regimen based on Clarithromycin. There are not many studies related to the use of furazolidone as a substitute for Clarithromycin in triple therapy regimens, so it is difficult to find previous studies. Furazolidone is a broad-spectrum nitrofurantoin antimicrobial drug (Mohammadi et al., 2017). In addition to the cost of the drug and its local availability, as with other variations of triple therapy regimens, Furazolidone is considered as a substitute for Clarithromycin in triple therapy because of resistance to the antimicrobials Clarithromycin, levofloxacin, and Metronidazole. This drug has previously been used in studies of *H. pylori* eradication in combination with other drugs as second-line or third-line treatment. One of the factors causing Furazolidone not to be widely used is the association of this drug with drug side effects, so Hajaghamohammadi et al. (2014) conducted a study with low-dose Furazolidone (Hajaghamohammadi et al., 2014).

*H. pylori* resistance to Clarithromycin varies in different countries and regions of the world. Research by Alba, Blanco and Alarcón (2017) found that *H. pylori* resistance to Clarithromycin is high in countries such as Spain, Italy, Iran, and the United States. Resistance exceeding 20% was found in Poland, Morocco, and Germany. Low resistance to Clarithromycin was found in Iceland (6%) and Indonesia (9%) (Alba et al., 2017). The research of Savoldi et al. (2018) found that in other countries such as Australia, resistance reached 96%, Vietnam with 63%, Israel with 47% and France with 43% (Savoldi et al., 2018). A bachelor's study investigated the drug resistance of Clarithromycin in the period from 2013 to 2020 in European countries. This study divides Europe into two regions, namely Northern Europe (Norway) and Southern Europe (Italy, Spain, and Greece). Resistance to Clarithromycin was greater in Southern European populations (28%) compared to Northern Europeans (7%). Research Bujanda et al. (2021) also studied the characteristics of patients who had taken Clarithromycin or not (non-naive/naive). Resistance to Clarithromycin is greater in patients non-naive (66%) compared to naive patients (25%) in the European population (Bujanda et al., 2021).

This study found the composition of the triple therapy regimen based on Clarithromycin replacement with the highest eradication rate (94.3%) in the Metronidazole-based triple therapy. These results were obtained from the research of Adachi et al. (2017) with the composition of Esomeprazole (2x20mg), Amoxicillin (2x750mg) and Metronidazole (2x500mg) for 7 days. However, this research still has some limitations such as There are fewer studies on variations in triple therapy regimens compared to studies on other *H. pylori* eradication regimens and most of the articles reviewed are from Iran so that researchers cannot discuss more widely about other countries. In addition, some articles had to be excluded because they did not include the criteria for the target population. This is



because the triple therapy regimen is preferred to treat *H. pylori* infection so that the population of patients with a single *H. pylori* infection is included in the study.

## CONCLUSION

From the results of this systematic review, it can be concluded that a variation of Metronidazole-based triple therapy is effective in dyspeptic patients with *H. pylori* infection. This can be seen from the eradication rate regimen which exceeds the target of 80%. Overall, the composition of the best triple therapy regimen was Metronidazole-based triple therapy for 7 days.

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