

# Current Diagnosis and Management of *Helicobacter pylori*

Nikko Darnindro\*, Ari Fahrial Syam\*\*

\* Department of Internal Medicine, Faculty of Medicine, University of Indonesia  
Dr. Cipto Mangunkusumo General National Hospital, Jakarta

\*\* Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine  
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

## ABSTRACT

*Helicobacter pylori* (*H. pylori*) is a microbe which cause chronic infection in human. Currently, the prevalence in developed countries continue to decrease, but the same does not happen in developing countries. Orofecal transmission and its connection with environmental condition is assumed to be its cause.

Impact of *H. pylori* infection in gastric mucosa is influenced by the bacteria pathogenesis which is able to survive in acid condition and causes inflammatory reaction. The diagnosis is differentiated through endoscopy or non-endoscopy depends on the alarm symptoms, local prevalence, pre-test probability, availability, cost and aim of examination.

Management of *H. pylori* depends on the high rate of clarithromycin resistance. In area with resistency prevalence below 20% triple therapy can still be used, while in increasing resistency area, use of four times daily therapy or other antibiotics such as levofloxacin and furazolidone can be considered.

**Keywords:** *Helicobacter pylori*, diagnosis, alternative therapy

## ABSTRAK

*Helicobacter pylori* (*H. pylori*) merupakan salah satu kuman yang dapat menyebabkan infeksi kronik pada manusia. Saat ini, prevalensi *H. pylori* di negara maju saat ini semakin menurun namun tidak demikian di negara berkembang. Transmisi oro-fekal dan keterkaitannya dengan kondisi lingkungan diperkirakan menjadi penyebabnya.

Dampak infeksi *H. pylori* pada mukosa lambung dipengaruhi oleh patogenesis kuman yang mampu bertahan dalam lingkungan asam dan menimbulkan reaksi peradangan. Diagnosisnya dibedakan secara endoskopi atau non-endoskopi bergantung dari adanya tanda bahaya, prevalensi di daerah tersebut, probabilitas pre-tes, ketersediaan, biaya dan tujuan pemeriksaan.

Tatalaksana *H. pylori* bergantung pada tingginya angka resistensi klaritromisin. Pada daerah dengan prevalensi resistensi di bawah 20% terapi triple masih dapat digunakan, sedangkan pada resistensi yang meningkat dapat dipertimbangkan penggunaan terapi quadruple atau antibiotik lain seperti levofloksasin dan furazolidone.

**Kata kunci:** *Helicobacter pylori*, diagnosis, terapi alternatif

## INTRODUCTION

Since the discovery of *Helicobacter pylori* (*H. pylori*) until now, this bacteria has been one of the microbes causing chronic infection to human. This bacterial infection is associated with several upper gastrointestinal complaints, such as chronic gastritis,

peptic ulcer, and gastric cancer.<sup>1</sup> Prevalence study performed in a private hospital in Jakarta showed decrease tendency in the prevalence of *H. pylori* infection from 12.5 % in year 1998 to 2.9% in year 2005.<sup>2</sup>

Risk factors of this *H. pylori* infection is strongly associated to socioeconomic status and living environment condition in early age. Other factors, including residents density, number of siblings, bed sharing, lack of flowing clean water are associated with high incidence of this bacterial infection. Bacterial transmission pattern, through which route bacteria can infect is still unclear. Human to human transmission through fecal or oral, or oral/oral exposure is the most possible way.<sup>3</sup> Till date, human is still the main infection site of *H. pylori*. Bacteria may survive in a long time underwater, which is proved by polymerase chain reaction (PCR) test in water reservoirs. Based on this findings, it is estimated that the transmission of *H. pylori* infection may happen through fecal-oral route, particularly in less hygienic water reservoirs, including swimming pool, raw vegetables or raw water consumption which are mostly found in developing countries.<sup>4</sup> Currently, although the infection prevalence seem to decrease in some countries, *H. pylori* still become an important factor in peptic ulcer, gastric cancer, and dyspepsia symptoms.

## DIAGNOSIS

As mentioned above that *H. pylori* is a microaerophilic bacteria living in extreme gastric environment, which is acidic. Bacteria has urease enzyme which can break urea into ammonia which is a base. Therefore, diagnostic procedure to prove the presence of *H. pylori* infection through direct method is very difficult, sometimes even requires endoscopic examination to obtain adequate specimen.<sup>1</sup>

Diagnostic method for *H. pylori* is divided into 2, which are: diagnosis using endoscopy or non-invasive diagnostic method which does not need endoscopy procedure. There is no single test which can completely be the gold standard for examination of *H. pylori*, therefore it needs correct considerations before choosing the diagnostic method to be performed. In choosing the test, some things need to be considered, including patients' clinical condition, the presence of alarm signs, the local prevalence of the disease, pretest probability of diagnostic tool, also the availability and cost from each test.

## ENDOSCOPIC DIAGNOSIS TEST

There are four tests which can be performed through endoscopy to diagnose *H. pylori* infection. These tests are rapid urease test (RUT), histology, culture and PCR.

## Rapid Urease Test

Rapid urease test (RUT) is a very specific diagnostic test for *H. pylori* and is used to detect bacteria through endoscopy.<sup>5</sup> RUT can detect the presence of *H. pylori* through urease activity. Through endoscopy, after gastric biopsy is performed, the result of biopsy is placed on an agar medium which has been given urea solution, buffer, and sensitive pH indicator. In the presence of *H. pylori*, urease enzyme found in this bacteria will metabolize urea into ammonia and bicarbonate causing increase in pH which will be detected by pH indicator in the form of colour changes. Result can be seen within 1 x 24 hours. There are several commercial RUT test which all in average has sensitivity of > 90% and specificity of > 95%.<sup>6</sup> Sensitivity of this test can be increased by obtaining more biopsy samples, either in number or places.<sup>5</sup> Study in Indonesia using an RUT testing tool (Pronto Dry) revealed sensitivity of 69.7% and specificity up to 95.7%.<sup>7</sup> Similar study using Pronto Dry test showed sensitivity up to 98.1% and specificity up to 100%.<sup>7</sup> Better results of sensitivity of the test may be influenced by several factors, including histopathology evaluation, biopsy standardization, both in location and number. This is proved by the fact that if the study only involved study in Jakarta and Bandung, the sensitivity may reach 95.7%.<sup>7</sup>

Treatment such as bismuth, antibiotic, and proton pump inhibitor may decrease microbe density and urease activity, which finally decrease the sensitivity of the RUT test. In a study, patient which received proton pump inhibitor drugs, sensitivity, specificity, positive predictive value and negative predictive value, this diagnostic test was 43.3%, 86.4%, 81.3%, 52.8% respectively, compared to patient who has not received proton pump inhibitor, values obtained were 71.9%, 80%, 82.1%, and 69%, respectively.<sup>5</sup> It was recommended to stop the drug at least a week before examination. In patient who has ever received antibiotic and proton pump inhibitor therapy, distribution of *H. pylori* in the stomach is separately discrete, predominant colony shift to the proximal. Therefore, it was advised to take biopsy sample from two locations, particularly the corpus and antrum angle for RUT diagnostic test. Other thing which can decrease the sensitivity of the examination is the presence of acute ulcer.

## Histology

Histology examination from biopsy sample has an important role in the diagnosis of *H. pylori*. In histologic examination, we found *H. pylori* directly, thus many

stated that this examination can be considered as gold standard. However, this is not entirely correct because there is still heterogeneity in biopsy methods, amount of biopsy, colouring, and the ability of pathologist.<sup>6</sup>

In histology examination to detect the presence of *H. pylori* in biopsy specimen, it is advised that specimen is taken from non-ulcer part. However in gastric ulcer patient, biopsy specimen can be taken from several location, including from the edge of the ulcer. Effectivity of specimen collection from ulcer edge is still controversial. Based on the report of a study on effectivity of histology examination in ulcer edge in patients with gastric ulcer without bleeding, it was concluded that histology examination from ulcer edge is inadequately sensitive for *H. pylori* diagnosis in gastric ulcer patients, particularly if ulcer is found in more proximal area or malignant ulcer.<sup>8</sup>

Due to the number of and density degree of microbes vary between individuals who has been exposed to treatment, biopsy is needed in enough amount for accurate diagnosis. It is suggested that at least 3 biopsy are taken from angle, major antrum curve, and major corpus curve.<sup>5</sup> Similar to RUT examination, sensitivity of this examination is based on previous treatment exposure. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy from histology examination decrease after exposure to acid inhibitor. After 4 weeks of omeprazole administration, microbe colony density in corpus and antrum decrease, but there is an increase in the density of colony in the fundus. Migration of *H. pylori* from antrum to the fundus is associated with decrease activity of gastric antrum.<sup>5</sup>

One of the advantages of this examination is that it can also evaluate pathological changes associated to *Helicobacter* infection, such as: signs of inflammation, atrophy, intestinal metaplasia or even signs of malignancy.<sup>6</sup>

### Culture

Culture is one of the specific diagnostic methods. It is not only important in finding *Helicobacter* bacteria, but it is also useful in testing the sensitivity of bacteria to antibiotic.<sup>6</sup> Nonetheless, culture is not a sensitive examination like RUT or even histology. Culture technique for *H. pylori* is difficult to perform and cause a huge cost. Difficulties in culture include it needs fresh sample and fixation has not been performed for histopathology examination. Inaccuracy in sample handling during transport may also cause negative false results. Sample is not allowed to contact with air and put inside saline solution (viable for 4 hours) or may

also be sent using particular semisolid agar medium.<sup>9</sup> Culture examination can be performed up to 24 hours after biopsy if sent using that particular medium.<sup>9</sup>

### Polymerase Chain Reaction

Polymerase chain reaction (PCR) is an examination which use DNA amplification technique to identify base arrangement in *H. pylori*. This diagnostic method is very specific and more sensitive compared to other endoscopic diagnostic tests.<sup>6</sup> Other advantage from PCR is it can detect the changes in DNA arrangement or mutation which is associated with resistency.

In their study, Weiss et al analyzed the effectivity of PCR examination to *Campylobacter like-organism* (CLO) test and immunohistochemistry. In the examination with gastric biopsy sample, all biopsy with positive CLO test and immunohistochemistry, positive results on PCR examination is also obtained. Even PCR can still detect patient who has negative results of CLO test and immunohistochemistry. Weiss et al also succeed in associating between PCR results with degree of inflammation due to *H. pylori*.<sup>10</sup>

### NON-ENDOSCOPY DIAGNOSTIC TEST

Currently there are three non-invasive diagnostic tests to detect the presence of *H. pylori*. Fecal test antigen, urea breath test (UBT), and antibody test can detect the presence of immunological reaction in infection, both in serum and urin.

#### Fecal Test Antigen

Fecal test antigen (FTA) detects the presence of *H. pylori* antigen in the faeces using anti *H. pylori* polyclonal antibody.<sup>6</sup> This faeces antigen examination is based on immunoassay technique through enzyme linked immunosorbent assay (ELISA). Currently, it is also been developed faeces antigen examination using monoclonal antibody. In *H. pylori* new antigen (catalase) has been found, which is more stable and examination using monoclonal antibody to this antigen can give out faster results, ranging around 70 minutes, also more specific compared to the method using polyclonal antibody.<sup>11</sup>

This test similar to UBT is useful in detecting active *Helicobacter* infection and helpful in the treatment evaluation. The use of this test with polyclonal antibody has good sensitivity, specificity, positive predictive value, and negative predictive value in examination before treatment, but not so good during therapy evaluation.<sup>6</sup> The use of monoclonal antibody has sensitivity, specificity, positive predictive value,

and negative predictive value more than 90% before and after treatment.<sup>6</sup> A study on validation of faeces antigen test with UBT as gold standard was performed in Brazil, in which 95 consecutive patients, who were both asymptomatic and experienced dyspepsia symptoms. Results of this study revealed the sensitivity reached 88% (95% CI = 75.7 - 95.5%) and specificity reached 87.5% (95% CI = 74.7-95.3%) with kappa index up to 0.75, therefore it was concluded that this faeces antigen test can be an alternative in UBT examination, particularly in developing countries.<sup>12</sup>

A study on faecal antigen test which is conducted in Indonesia using HpSA test with cut off point 0.27 obtained sensitivity 66.7% and specificity 78.9%. Results of this test can be used for diagnosis because the specificity approached the specificity of other test, but cannot be used for screening due to its low sensitivity.<sup>13</sup>

In examination in low probability pretest community, FAT has better accuracy rate compared to antibody examination. Nonetheless, similar to UBT, this test is so much influenced by the use of bismuth, antibiotic, and proton pump inhibitor. FAT specificity also decrease in patients with bleeding peptic ulcer, therefore, single diagnostic test is not recommended.<sup>6</sup>

### Urea Breath Test

Urea breath test (UBT) can be considered as one of the gold standard examinations for *H. pylori* through endoscopy. Similar to RUT, UBT is helpful in identifying active infection of *H. pylori* through urease activity. With the presence of *H. pylori*, urea compound which has been labelled with <sup>13</sup>C non-radioactive isotope or even <sup>14</sup>C radioactive isotope will be metabolized by urease to produce labelled CO<sub>2</sub> compound, which can be counted quantitatively. <sup>13</sup>C non-radioactive isotope will be a choice to be used in female and children.<sup>6</sup>

For after treatment evaluation, UBT also give out good and accurate result. Therefore, similar to RUT, this test is very influenced by previous treatment and thus, it was suggested to stop the use of bismuth and antibiotic at least 28 days and proton pump inhibitor 1–2 weeks before UBT is performed.<sup>6</sup> By stopping proton pump inhibitor in 2 weeks before UBT, it is expected that there is regrowth of bacteria.<sup>14</sup> Regarding administration of H<sub>2</sub> receptor antagonist is still controversial, however several laboratories suggested drugs cessation 24-48 hours before examination is performed. Use of citric acid before labelled urea consumption may help decrease false negative.<sup>14</sup> Citric acid can inhibit gastric emptying and decrease

gastric pH. Unlike proton pump inhibitor and H<sub>2</sub> antagonist, antacide need not to be discontinued as it does not effect this examination.<sup>14</sup> Besides influenced by previous drug use, the weaknesses of this test are costly and requires special equipment.

### Antibody Test

Antibody test is one of the non-invasive diagnostic tests based on the detection of specific IgG antibody to *H. pylori*.<sup>6,14</sup> IgG antibody appears approximately 21 days after *H. pylori* infection and can stay in quite long time. Antibody to *H. pylori* can be measured quantitatively using ELISA technique, reverse flow immunochromatography or passive hemagglutination. The advantages of this examination in addition to the cost is not too high, it is widely available and results can be obtained in short time. Furthermore, antibody test is the only diagnostic tool which is not influenced by local changes in the stomach due to the use of drugs, therefore it is not required to stop therapy given to overcome gastrointestinal symptoms, including bismuth, proton pump inhibitor or antibiotic use. Nonetheless, there is factor which limits the use in the community, such as the positive predictive value is influenced by disease prevalence in the community.<sup>14</sup> In community with low prevalence, the positive predictive value is also low. Another common problems are the antigen type being used in an area differs to the other area, therefore it cannot be used in other location.

Serology diagnostic test of *H. pylori* with local antigen in Indonesia has been produced in laboratories in Mataram, West Nusa Tenggara. Diagnostic test with equipment developed by Sumohardjo et al using local antigen obtained sensitivity of 96% and specificity 85.7%.<sup>15</sup> Epidemiology study using this tool has been conducted in Jakarta and resulted that the prevalence of *H. pylori* reaching 52.3%.<sup>7</sup>

### Urine Antibody

*H. pylori* antibody examination from urine is reported to be one of the diagnostic tests which is reliable for adults. The base of this examination is the finding of *H. pylori* antibody in body liquid other than serum. IgA antibody *H. pylori* can be found in gastric secretion of patients who are infected with *H. pylori*. IgA and IgG *H. pylori* antibody can be found in saliva and gastric secretion. IgG *H. pylori* antibody in urine can also be found and its association with *H. pylori* in human.<sup>16</sup> However, level of *H. pylori* antibody in urine is much more lower compared to its level in the serum. This low level causes the test depend on the patients' kidney function, urine sediment, and urine pH.



Urine antibody test method using immunoassay method obtained sensitivity and specificity reaching 95.9% and 90%.<sup>16</sup> Several fear regarding the influence of proteinuria to sensitivity and specificity of this tool is disproved through the study performed by Yamamoto et al, which showed that accuracy rate still above 95% if used in patients with proteinuria.<sup>17</sup>

## MANAGEMENT OF *HELICOBACTER PYLORI*

Management with triple therapy is still the main treatment for *H. pylori* infection. Besides triple therapy, four times daily therapy can also be used in region with high resistency of clarythromycin. Based on the therapy guidelines in United States, triple therapy uses proton pump inhibitor, clarythromycin, and amoxicillin or metronidazole for 14 days, while four times daily therapy uses H2 receptor antagonist, bismuth, metronidazole, and tetracycline for 10-14 days.<sup>6</sup> Consensus on treatment of *H. pylori* in Europe also recommend combination therapy of proton pump inhibitor (PPI)-clarythromycin and amoxicillin or metronidazole in region with clarythromycin resistency rate below 15–20%.<sup>14</sup> Generally, there is decrease in the efficacy of this clarythromycin based triple therapy, which may be caused by adherence, high level of gastric acidity, high bacterial colony, microbe strain type, and most important is resistency of *H. pylori* to clarythromycin. Resistency to clarythromycin increases globally. In Europe, resistency rate increases from 9% in 1998 to 17.6% in 2008-2009. This resistency rate increases almost in all part of Europe, however in some places such as Middle, West, and South Europe, the resistency increases more than 20%.<sup>14</sup> In regions where it has been known that the resistency rate exceeds 15–20% administration of clarythromycin based therapy need to be avoided.

Alternative therapy which can be given to patients with *H. pylori* infection beside clarythromycin-based therapy and bismuth-based therapy is sequential therapy. This therapy can be used particularly if first line antibiotic has been given or there is previous exposure to that antibiotic, or it has been known that the resistency rate to clarythromycin exceeds 20%.<sup>14</sup>

As has been mentioned above that recommended first line therapy in United States are clarythromycin-based and four times daily-bismuth therapy. If used properly, the eradication rate may reach 70-80%.<sup>6</sup> In triple therapy other than using PPI and clarythromycin, in combination with second antibiotic which is

amoxicillin is also used. However, as we know that the wide use of amoxicillin particularly as antibiotic in the management of upper respiratory tract infection, it is also be feared that resistency to amoxicillin may happen. Thus, amoxicillin may be substituted by metronidazole. Use of amoxicillin or metronidazole has similar effectivity. In a meta-analysis comparing eradication therapy by using PPI-clarythromycin-amoxicillin and PPI-clarythromycin-metronidazole revealed equivalent eradication rate (71% vs. 65%) which is statistically not significant.<sup>18</sup> Hence, as second antibiotic in triple regimen therapy, amoxicillin or metronidazole can be used depend on the local resistency pattern.

To increase eradication rate, it is suggested to increase of proton pump inhibitor dose to be twice daily high dose. Meta-analysis of 13 studies revealed that use of proton pump inhibitor twice daily in clarythromycin-based therapy was more effective compared to once daily dose one. This study exhibited that the use of high dose PPI can increase recovery (cure) rate of 6–10% compared to the standard dose.<sup>14</sup> History of routine consumption of PPI before diagnosis of *H. pylori* does not change the duration and dose of therapy which will be given. However, in patients who were proved to suffer from intolerance to PPI, H2 receptor antagonist can be given in substitute.

Treatment duration also become an important thing in eradication of *H. pylori* infection. Lengthening of treatment duration from 7 days to 10-14 days is said to increase eradication rate, but in the other hand increase health cost. Study using combination of rabeprazole, clarythromycin, and amoxicillin failed to show significant difference of eradication rate by lengthening duration of treatment from 7 to 10 days (77% vs. 78%).<sup>20</sup> However, another meta-analysis comparing treatment duration of 7 and 14 days using triple therapy concluded that lengthening duration for 14 days might increase eradication rate.<sup>19</sup> Maastricht IV Conference in Europe also summarized that lengthening treatment duration to 10-14 days may increase eradication rate up to 5-6%.<sup>14</sup> Therefore, although some things need to be considered, including cost, adherence, and arising side effects, it is suggested that treatment is administered for 14 days.

**Table 1. First line regiment of *Helicobacter pylori* eradication<sup>6</sup>**

Regiment	Duration	Eradication rate	Comments
PPI twice daily, clarythromycin 500 mg twice daily, amoxycillin 1000 mg twice daily	10–14 days	70–85%	In patients who has never received macrolide, not allergic to penicillin
PPI twice daily, clarythromycin 500 mg twice daily, metronidazole 500 mg twice daily	10–14 days	70-85%	In patients allergic to penicillin, intolerant to bismuth
Bismuth 525 mg four times daily, metronidazole 250 mg twice daily, tetracycline 500 mg four times daily, ranitidine 150 mg twice daily atau PPI fourth-twice daily	10–14 days	75-90%	In patients allerhic to penicillin
PPI + amoxycillin 1 g twice daily are recommended PPI, clarythromycin 500 mg twice daily, tinidazole 500 mg twice daily	5	> 90%	

PPI: proton pump inhibitor

Use of four times daily therapy as an alternative to three times daily therapy is proved in a meta-analysis study. Comparison of three times daily and four times daily therapy, either per protocol (85% vs 87%) or intention to treat (79% vs 80%) showed there was no significant difference through statistic in the ability to eradicate *H. pylori*.<sup>21</sup> One of the difficulties of using four times daily therapy associated with the amount and duration of treatment administration. Frequency of moderate to severe side effect occurrence in bismuth therapy administration is not more common compared to clarythromycin-based therapy.<sup>21</sup>

Both first line therapy above seem to be quite promising in *H. pylori* eradication, however the eradication rate in studies mentioned above generally showed less than 85%.<sup>6</sup> Therefore, alternative therapy is developed, which was sequential therapy. Multicentre study in Taiwan which compared 10 days, 14 days sequential therapy, and 14 days three times daily therapy showed although there was no difference statistically, sequential therapy has better eradication rate (90.7% vs. 87% vs. 82.3%).<sup>22</sup>

Eradication of *H. pylori* often failed, this is influenced by patients' adherence or even bacteria resistency. When confronted with treatment failure, antibiotic administration in the previous regiment was advised to be avoided. Due to the high cost and rare availability, culture and sensitivity test is not performed, unless there is failure in at least two regiments of therapy.

Resistency become one of the most important thing in therapy failure. Multicentre study in United States between 1998 to 2002 obtained metronidazole resistency rate of 25% compared to clarythromycin resistency rate of 13%.<sup>23</sup> Although metronidazole resistency rate is higher, therapy failure is mostly caused by clarythromycin resistency. Metronidazole resistency is more relative, which is a resistency which can be resolved by increasing the dose of metronidazole or change regiment if therapy into four times daily regiment.<sup>6</sup> From a study, it is stated that in

patient infected with metronidazole resistant bacteria who received four times daily therapy actually still has eradication rate exceeding 80%, which was 80.4% compared to if previously not proven to be infected with metronidazole resistency, in which eradication rate can reach 87.7%. In patient with clarythromycin resistant bacteria, the use of clarythromycin-based therapy eradication rate decreases into 21.4%.<sup>24</sup>

Therapy regiment most frequently used is the clarythromycin-based therapy, therefore failure therapy with this regiment can be resolved with administration of bismuth four times daily regiment, consisting of PPI, tetracycline, metronidazole, and bismuth. Based on the guidelines published by European Helicobacter Study Group (EHSg) and Maastricht IV consensus stated that four times daily therapy using bismuth, including second line therapy, and used effectively in patients with first line treatment failure. Bismuth four times daily can also be used as first line in region with high rate of clarythromycin resistence.<sup>14</sup> But, as has been mentioned above that the weakness of bismuth regiment therapy is the more number of pills, more frequency administration, and more frequent occurrence of side effects.

#### **Alternative Treatment of *Helicobacter pylori***

Second line therapy which can be used other than bismuth is the use of rifabutin, an antibiotic which has long been used in tuberculosis treatment known to be useful as an alternative to clarythromycin. A study in Australia involving 130 patients failed with clarythromycin-based treatment, received rifabutin 150 mg, pantoprazole 80 mg, and amoxycillin 1-1.5 g per day for 12 days. Eradication rates in intention to treat and per protocol with this regiment reach 90.8% and 90.8%, respectively.<sup>25</sup> The most common side effects which occur from rifabutin administration are rash, gastrointestinal symptoms, including nausea, vomiting, dyspepsia, and diarrhea.<sup>25</sup>

Furazolidone, antibiotic often used in management of giardiasis, cholera, and bacterial enteritis also play role as an alternative to clarythromycin, metronidazole,

and amoxicillin.<sup>6</sup> Furazolidone has bacteriostatic and bactericidal to negative and positive gram bacteria, also absorbed well in gastrointestinal tract. This drug also has activity to *H. pylori* and till date, furazolidone resistency strain of bacteria is still rare to be found, therefore, this drug is a potential option to treat failure in *H. pylori* treatment.<sup>26</sup> Other drugs which can be used as an alternative treatment are levofloxacin, fluoroquinolone group antibiotic which through invitro proved to have activity to *H. pylori*. Combination of PPI, levofloxacin, and amoxicillin which has been evaluated as second and third line treatment in management of *H. pylori*. Meta-analysis study on the use of levofloxacin based and four times daily therapy in patient who failed with first line therapy resulted that the use of levofloxacin based therapy for 10 days is more effective compared to 7 days (81% vs. 73%;  $p < 0.01$ ).<sup>27</sup> From this meta-analysis, eradication rate in levofloxacin-based and four times daily therapy also has been evaluated. Statistically, there is no significant difference, but levofloxacin based therapy has better eradication rate (81% vs. 70%; OR = 8; 95% CI = 0.94-3.46). If evaluated from the arising side effects, levofloxacin-based therapy has lower side effects (95% CI = 0.16-0.46; OR = 0.27).<sup>27</sup> Therefore, it can be concluded that levofloxacin-based therapy can be used as an alternative therapy or therapy for those who failed with the first line. Further, in Brazil, it has also been administered combination therapy of furazolidone, levofloxacin, and lansoprazole as treatment choices in cases where initial treatment of *H. pylori* failed. In a study involving 48 patients, performed per protocol and intention to treat analysis showed eradication rate reached 89% and 88% even in patients who failed initial treatment and were given this combination, eradication rate reached 100%.<sup>26</sup> Therefore, combination of these three drugs can be chosen in failure of first line treatment of *H. pylori* particularly in new patients who experienced one time failure.

As has been mentioned above regarding the increase of resistency rate to clarythromycin and metronidazole caused decrease in eradication rate of three or four times daily regiment administration.

Therefore, currently sequential regiment has been used, particularly 10 days regiment therapy administration, divided into first 5 days therapy with proton pump inhibitor and amoxycillin 1 g twice daily continued with 5 days clarythromycin 500 mg twice daily and tinidazole 500 mg twice daily. Administration with this method is expected to increase the treatment success rate because initial administration of amoxycillin will help to weakened bacterial cell wall which will decrease resistency to clarythromycin.

In a study which tried to compare this sequential regiment with three times daily therapy for 7, 10, and 14 days, it was found that eradication rate with sequential therapy reached 82%, compared to three times daily therapy for 7, 10, and 14 days which reached 75.7%, 81.9%, and 84.4%, respectively.<sup>28</sup> From this result, there was no significant difference on the eradication rate, thus the use of sequential therapy could be used to prevent the increasing resistency rate to clarythromycin and metronidazole.<sup>28</sup>

Other studies as mentioned above regarding comparison of sequential regiment for 14 days, three times daily therapy for 7 and 14 days also did not showed statistical difference, although sequential therapy has better eradication rate compared to triple therapy administration, which were 90.7% and 87% compared to 82.3%.<sup>22</sup> From both studies above, it can be concluded that sequential therapy can be a chance for main treatment of *H. pylori*.

Evaluation on results of treatment is important to be performed for further treatment and management of the patient. Not all patient who undergo treatment have to experience eradication test. Bacterial eradication test is performed in patients with *H. pylori* with ulcer, patient who underwent gaster resection, patient with mucosa-associated lymphoid tissue (MALT) lymphoma, and patient with dyspepsia complaints which did not subside after test-and-treat strategy. After treatment administration, eradication need to be confirmed with UBT or FAT.<sup>29</sup> Monitoring of this treatment is performed 4 weeks after treatment is completed.<sup>29</sup> Serology antibody test cannot be used to evaluate therapy because IgG which is the basis of the examination can last for a long duration.

**Table 2. Second line therapy in persistent *Helicobacter pylori* based on Maastricht IV Consensus<sup>6</sup>**

Regiment	Duration	Eradication rate	Comments
PPI four times daily, tetracycline, pepto-bismol, metronidazole four times daily	7	68% (95% CI = 62-74%)	Affordable, easy retrieved, but more frequent consumption and more number of pills
PPI, amoxycillin 1 g twice daily, levofloxacin 500 mg four times daily	10	87% (95% CI = 82-92%)	

PPI: proton pump inhibitor

While in certain cases, such as gastric ulcer and MALT lymphoma, monitoring is performed through endoscopy and tissue biopsy.

## CONCLUSION

*H. pylori* is a chronic infection in gastrointestinal which is responsible to the emergence of upper gastrointestinal tract complaints. Disease detection and prompt treatment are needed to decrease morbidity and prevent the development of malignancy. Current available modality therapy received huge challenge, which is the developing resistency rate to standard therapy of *H. pylori* infection, therefore alternative therapy is needed to eradicate the disease.

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*Correspondence:*  
*Ari Fahrial Syam*  
*Division of Gastroenterology*  
*Department of Internal Medicine*  
*Dr. Cipto Mangunkusumo General National Hospital*  
*Jl. Diponegoro No. 71 Jakarta Indonesia*  
*Phone: +62-21-3153957 Facsimile: +62-21-3142454*  
*E-mail: ari\_syam@hotmail.com*

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