

Prevalence of Antibiotic-Resistant *Helicobacter pylori* and The Effect on Standard Treatment

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INTRODUCTION

Helicobacter pylori infection is one of the most common infections in human worldwide. Chronic infection of *H. pylori* leads to multiple alimentary diseases including gastric inflammation, atrophic gastritis, peptic ulcer, gastric cancer and gastric mucosa-associated lymphoid-tissue (MALT) lymphoma⁽¹⁾. Prevalence of *H. pylori* infection rate has geographic variation which there is a higher prevalence in developing countries including Thailand⁽²⁾.

It has been found that the infection prevalence is declining⁽³⁾. However, the eradication rate of recommended standard treatment is decreasing as well. American College of Gastroenterology on the management of *H. pylori* infection in 2007 recommends a triple therapy regimen, which consists of a proton pump inhibitor (PPI) and two combined antibiotics (clarithromycin, amoxicillin or metronidazole) as a first-line treatment⁽⁴⁾. Likewise, the Second Asia-Pacific Consensus guideline for *H. pylori* infection recommends the same regimen⁽⁵⁾. Emerging of *H. pylori*-antibiotic-resistant strains may affect the efficacy of this standard regimen. Systemic review conducted by Mégraud in 2004 showed that the *H. pylori* resistance to clarithromycin or metronidazole significantly decreased the eradication rate of standard PPI-based triple therapy⁽⁶⁾. Since the rate of *H. pylori* resistance is varying on geographic region, choosing the appropriate

antibiotic depends on the local resistance rate in each area.

Prevalence of *H. pylori* resistance to clarithromycin

The primary resistance rate of *H. pylori* to clarithromycin is different among each region of the world. The overall global resistance from a systemic review in 2004 was 9.9% (95% CI 8.3-11.7)⁽⁶⁾. An another systemic review, which recruited a number of published studies during 2006 to 2009, reported 17.2% (95% CI 16.5-17.9) of primary clarithromycin resistance⁽⁷⁾. In Europe, Mégraud⁽⁶⁾ found that there was significant difference of resistance rate according to different parts. The resistance in the Northern Europe was low rate which was 4.2% (95% CI 0-10.8). The Central/Eastern Europe resistance rate was 9.3% (95% CI 0-22), while the rate was the highest in the Southern Europe which was 18% (95% CI 2.1-34.8). In North America, the resistance rate in USA (1993-1999) was 10.6-12.6%⁽⁸⁻¹⁰⁾ and it was less than 4% in Canada (2000)⁽¹¹⁾. Asia, like Europe, had varying rates of resistant *H. pylori* strains according to different countries. The highest resistance rate was in Japan and the lowest rate was in Korea and Thailand. Japan had increasing resistance from 19% in 2002 to 28% in 2005⁽¹²⁾. Hong Kong (a study in 2000) and Taiwan (a study in 2007) had similar resistance rates which were

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10.8%⁽¹³⁾ and 13.5%⁽¹⁴⁾ respectively. Korea had a lower rate but increased from 4.8% in 1994 to 7.7% in 1999⁽¹⁵⁾. A nationwide survey of *H. pylori* resistance in Thailand during 2004-2012 found that the resistance to clarithromycin was 3.7%⁽¹⁶⁾ which was decreasing from 19% (a study in 2001)⁽¹⁷⁾. Moreover, a study of risk factor for *H. pylori* resistance in USA found that metronidazole resistance was associated with older age, female sex and inactive ulcer disease⁽¹⁸⁾.

Clarithromycin-resistant *H. pylori* decreases efficacy of an antibiotic regimen which contains clarithromycin. It was found that the eradication rate was 87.8% when strains were clarithromycin susceptible compared with 18.3% when strains were clarithromycin resistance with OR 24.5 (95% CI 17.2-35.0)⁽⁶⁾. Since clarithromycin needs to bind to ribosome in order to kill *H. pylori*, resistant *H. pylori* strains are associated with failure to bind with to ribosomes. Thus, clarithromycin resistance cannot be overcome by dose or duration increasing⁽¹⁹⁾.

Prevalence of *H. pylori* resistance to metronidazole

The prevalence of *H. pylori* resistance to metronidazole, like clarithromycin, geographically varies among countries around the world. The overall global resistance was 26.7% (95% CI 25.2-28.1)⁽⁷⁾. In the European multicenter study in 1988, the metronidazole resistance was 33.1% (95% CI 7.5-58.9). There was no significant difference between the North (33% (95% CI 7.1-69.2)) and South (40.8% (95% CI 27.3-54.3)) but it was significantly lower in the Central and Eastern parts of Europe (29.2% (95% CI 17.2-35.0))⁽²⁰⁾. USA had the resistance rate of 21.6% (1993-1999)⁽¹⁰⁾. Prevalence of *H. pylori* resistance to metronidazole in Asia is contrast to clarithromycin. It is much lower in Japan, while higher in other parts of Asia such as Korea and Hong Kong. Japan had resistance rate of 3.3-5.3% during 2002-2005⁽¹²⁾. In Korea, the overall resistance was 40.5% in 1994-1999⁽¹⁵⁾. In Hong Kong, a single study showed that the prevalence was 49.4%⁽¹³⁾. Likewise, studies in Thailand showed the high rate of resistance that was 30-36%^(16,17,21). In addition, female sex significantly had more metronidazole-resistant *H. pylori* strains which may be a result of more frequent exposure to metronidazole for gynecologic infection treatment⁽¹⁸⁾.

Metronidazole is a prodrug that needs enzyme of *H. pylori* to activate the drug to become an active form

within cell. There are a number of different enzyme pathways involving this process. Thus, the resistance can be overcome by increasing the dose or duration of the drug⁽¹⁹⁾.

Prevalence of *H. pylori* resistance to amoxicillin

Prevalence of *H. pylori* resistance to amoxicillin is similar among countries worldwide. Besides, it is much lesser than clarithromycin or metronidazole resistance. They were 0.8% (95% CI 0-8.9) in Europe⁽²⁰⁾, 1.4% (95% CI 1-1.8) in USA⁽¹⁸⁾, 0.3% in Japan⁽²²⁾, 0.3% in Hong Kong⁽²³⁾ and 0% in Korea⁽¹⁵⁾. In Thailand, the resistance rate was higher than other countries. A nationwide survey of Thailand in 2004-2012 found the resistance rate of 5.2%⁽¹⁶⁾.

As the amoxicillin resistance rate is low, it may not be clinically significant. Treatment success of triple therapy containing amoxicillin is not always affected by amoxicillin-resistant strains⁽¹⁹⁾.

Prevalence of *H. pylori* resistance to tetracycline

The resistance rate of *H. pylori* to tetracycline is also low. The overall global resistance was 5.9% (95% CI 4.7-7.1)⁽⁷⁾. Among European countries, the prevalence rates were not significantly different with average of 2.1% (95% CI 1.1-3.5)⁽⁷⁾. On the contrary to Asia, the resistance rate was varied. It was high in Korea which was 5.3%⁽¹⁵⁾, while the resistance rate in Taiwan was low (0.5%)⁽¹⁴⁾. In Thailand, it was a wide range of resistance rate. A study in dyspeptic patients in 2002 found the rate of 5.1%⁽¹⁷⁾. Another study in 2008 and a nationwide survey of Thailand during 2004-2012 reported the same rate of 1.7%^(16,21).

Prevalence of *H. pylori* resistance to levofloxacin

There are a limited number of studies on the prevalence of levofloxacin resistance. In Europe, it was 10.6% in Italy⁽²⁴⁾ and 7.5% in United Kingdom⁽²⁵⁾. In Asia, it was 14.9% in Japan⁽²⁶⁾, 11.9% in Taiwan⁽²⁷⁾, 12.4% in Korea⁽²⁸⁾, and 11.5% in Hong Kong⁽²⁹⁾. In Thailand, it was 7.2% for levofloxacin⁽¹⁶⁾ and it was 7.7%⁽¹⁶⁾ and 9.2%⁽¹⁶⁾ for ciprofloxacin.

Levofloxacin containing regimen for *H. pylori* eradication therapy is recommended as a salvage treatment after primary failure of triple therapy by both American College of Gastroenterology guideline⁽⁴⁾ and the Second Asia-Pacific consensus⁽⁵⁾. However, high prevalence of *H. pylori* resistant rate in some parts of the world may affect the efficacy of this salvage therapy.

Impact of antibiotic-resistant *H. pylori* to efficacy of standard treatment

A standard triple regimen contains a proton pump inhibitor and two out of three antibiotics (amoxicillin, clarithromycin, and metronidazole). It is recommended by American College of Gastroenterology guideline and the Second Asia-Pacific consensus for *H. pylori* treatment. Since prevalence of antibiotic-resistant *H. pylori* strains in many countries is increasing, the efficacy of this regimen can be reduced.

Metronidazole-resistant *H. pylori* strains can affect on efficacy of OMA (omeprazole, metronidazole, amoxicillin) and OMC (omeprazole, metronidazole, clarithromycin) regimen differently. Meta-analysis from 93 studies with 10,178 participants⁽³⁰⁾ found that metronidazole resistance reduced the efficacy of OMA by 30% (95% CI 21.8-38.2) in the absence of clarithromycin resistance. The mean efficacy of the OMA in the presence of metronidazole resistance was only 63% (95% CI 55.6-70.2). On the contrary, metronidazole resistance decreased the efficacy of OMC regimen by only 18% (95% CI 13.1-23.3). The mean eradication rate of OMC was higher which 72% (95% CI 66.0-76.2) if *H. pylori* was metronidazole-resistant strain. Likewise, clarithromycin resistance affects the efficacy of OCA (omeprazole, clarithromycin, amoxicillin) and OMC (omeprazole, metronidazole, clarithromycin) regimen as well. In OCA regimen, the efficacy decreased by an estimated 66% (95% CI 58.2-74.2) and the eradication rate ranged from 0% to 50%. In OMC regimen, clarithromycin resistance reduced efficacy by 35% (95% CI 26.4-46.4) and the mean efficacy of this regimen was 51% (95% CI 41.5-60.4). If the resistance of both clarithromycin and metronidazole was present, the eradication rate of OMC regimen would be extremely decreased to only 13% (95% CI -22.4-48.8).

In summary, one antibiotic resistance either clarithromycin or metronidazole alone has varied effect on efficacy of triple therapy. Clarithromycin resistance affects on the success of therapy the most while the treatment with OMC has the highest eradication rate in the presence of metronidazole resistance. Moreover, presence of dual clarithromycin-metronidazole resistance dramatically reduced the efficacy of therapy containing clarithromycin and metronidazole. It is recommended to shift to another alternative regimen.

CONCLUSION

Emerging of antibiotic-resistant *H. pylori* strains is found all over the world. This situation is clinically important and affects the efficacy of standard treatment in clinical practice. Prevalence of antibiotic-resistant *H. pylori* is geographically different among countries worldwide. Physicians should be aware of local resistance prevalence in each area and choose the most appropriate regimen.

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Suchartlikitwong S, et al.

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