Recent Updates of *Helicobacter pylori* Infection: from Epidemiology Study to Guideline Issues

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ABSTRACT

Helicobacter pylori (H. pylori) infection is still a big issue in gastroenterology field. Its relationship with gastrointestinal malignancies now is widely known and the extra-gastrointestinal manifestation of this epidemic bring new problems. Although the prevalence is decreasing in developed countries, the resistance rate of some strains to standard therapy needs more attention and new strategies. Recent epidemiology studies revealed that H. pylori infection is a specific population disease. Many trials and meta analyses revealed new evidences and horizons in the management of this infection. This review updated and highlighted pathophysiology, clinical aspect, and new epidemiology data on H. pylori infection which is published in the last five years.

Keywords: *Helicobacter pylori, update, epidemiology*

ABSTRAK

Infeksi Helicobacter pylori (H. pylori) masih merupakan permasalahan besar di bidang gastroenterologi. Hubungannya dengan keganasan saluran cerna saat ini telah dikenal secara luas dan manifestasinya di luar pencernaan pada epidemi ini membawa masalah baru. Meskipun prevalensinya menurun di negara-negara maju, namun tingkat resistensi dari beberapa terapi standar membutuhkan lebih banyak perhatian dan strategi baru. Penelitian epidemiologi baru-baru ini mengungkapkan bahwa infeksi H. pylori didapatkan pada populasi tertentu. Banyak percobaan dan metaanalisis yang mengungkapkan bukti dan wawasan baru dalam penatalaksanaannya. Ulasan ini memperbarui dan menyoroti patofisiologi, aspek klinis, dan data epidemiologi baru pada infeksi H. pylori yang telah dipublikasikan dalam lima tahun terakhir.

Kata kunci: *Helicobacter pylori, memperbarui, epidemiologi*

INTRODUCTION

Infection of *Helicobacter pylori (H. pylori)* is still a big problem in some areas.[1,2] Not only dyspeptic symptoms that increase the number of consultation and referral to gastroenterologist and health cost, the risk for ulcers, gastric lymphoma, and gastric cancer also increase.[3] Furthermore, *H. pylori* infection is reported to be associated with many extra-gastrointestinal manifestations, such as idiopathic thrombocytopenic purpura (ITP), unexplained iron deficiency anemia, cardiovascular disease (ischemic heart diseases), neurological disorders (i.e. stroke, Parkinson's disease, Alzheimer's disease), obesity, and skin disorders.[4] From the discovery of *H. pylori* in 1983 as quoted by Fock et al, this infection has been recognized to be a global health problem.[5] But, since the test of this infection is not easy and needs special tools, we are challenged to prove how big the problem in specific population is. It will impact the clinical recommendation and policy for screening and eradication programs.

From old literatures, it has been said that the prevalence of *H. pylori* infection in developing countries is higher than in developed countries.[6-8] Prevalence in developed countries is 30-40% while in developing countries the prevalence reaches 80-90%. About 10-20% from all infection will develop to gastroduodenal problems. In non-ulcer dyspepsia patients, the prevalence of *H. pylori* infection varies from 20-40% based on the diagnostic methods used in the study; serology, culture, or histopathology.[6] In a multicenter study from Indonesia, from 550 dyspeptic patients who underwent endoscopy, *H. pylori* was found positive in 56 (10.2%) patients. The highest prevalence of *H. pylori* was found in patients from Jogjakarta (30.6%) and the lowest was in patients from Jakarta (8%).[9]

The correlation between *H. pylori* infection and gastric cancer is also a big concern.[10] Global epidemiologic studies revealed that geographical differentiation influence the correlation between *H. pylori* infection and development of gastric cancer.[10,11] Many studies and reviews already proved and discussed about this phenomenon. We can resume that there are many factors, protective and predisposing, that lead to gastric cancer other than *H. pylori* infection itself, but still, the infection have an important role.[12]

Many developments in the field of *H. pylori* infection today endorse hundred studies all over the world to search new pathogenesis model, epidemiology phenomenon, best diagnostic and treatment for reducing the risk of malignancy complication in the latter day. All of these findings need efforts, hardwork, and dedication from researchers, clinicians, andepidemiologists. In fact, researches in this field never stop in the last 20 years.

THE LIFE OF *HELICOBACTER PYLORI* IN HUMAN BODY

H. pylori can be called one of the most successful bacteria live in human because it survives from the most difficult situation, and colonizes in one half of the human population. Salama et al published the latest pathogenesis review about persistence strategies of *H. pylori* in humans' stomach.[13] In the review, they discussed the pathogenesis of this microorganism and the mechanisms it uses to colonize gastric mucosa. They focus on the role of the virulence factors vacuolating cytotoxin A (VacA), cytotoxin-associated gene A (CagA), and cytotoxin-associated gene L (CagL), and describe the immunobiology of *H. pylori* infection. Besides virulence factors, these bacteria also manipulates the innate and adaptive immune systems of the host to promote its own persistence.[13]

The stomach is a hard niche for microorganism to live. *H. pylori* adheres to epithelial cells by producing adhesin. Adhesin binds to carbohydrate and lipid in epitelial cell membrane. *H. pylori* can only survive for a while (in minutes) in the lumen and must move to gastric epithelial surface. Urease enzyme produced by the bacteria raised the pH in the stomach to near neutral and the viscoelastic solution allowing *H. pylori* to live actively in the human gaster. The helical shape also enhanced the motility throughout this media. *H. pylori* also actively manage its interaction with the host epithelium to escape from the clearance by inflammation responses.[13-15]

Only few number of studies and reviews discuss the strategies of *H. pylori* to promote survival to face immune system. *H. pylori* creates proteins which neutralize reactive oxygen species.[13] The microorganism also produces arginase to inhibit nitric oxide production by macrophage, neutrophil, and epithelial cell-derived nitric oxide synthase. By complex-genetic diversification, *H. pylori* also regulates natural ability to become more persistent, which is called chronically persistence, in the human stomach.[13,14]

Strains of *H. pylori* manipulate host tissues and give persistence in the epithelial cells of the gaster by secreting toxins. Two most important toxins produced are VacA and CagA.[14] While VacA gene determines the severity of infection of the bacteria, CagA is dominant to give risk for gastric cancer to the patient. CagA acts as oncogenic protein and also have a vital role in colonization of *H. pylori*. The virulence of the microorganism depends on these proteins. Latest studies in the field of molecular gastroenterology give attention to the VacA and CagA interaction as one of the most important 'missing link' for the oncogenesis of gastric lymhoma and gastric cancer.[13]

Salama et al also reported the way of *H. pylori* elaborate strategies to evade and subvert host immune defences. *H. pylori* can avoid detection by several types of pattern recognition receptors (PRRs) which are very crucial for recognition of gram-negative enteropathogens.[13] Two mechanisms used by this bacteria are evasion of innate immune detection by pro-inflammatory toll-like receptors (TLRs) and the preferential activation and manipulation of antiinflammatory TLRs and CLRs (C-type lectin receptors). All of these strategies make *H. pylori*

stronger and persist in the stomach, as well as more virulence and tend to higher the risk of malignancies in human gastrointestinal tract.[15]

WHAT EPIDEMIOLOGIC STUDIES TELL US ABOUT?

By searching database of medical publications, in only one year, there are not less than 25 new publications concerning about epidemiologic studies of *H. pylori* infection all over the world. Several things can be concluded from all of the studies: 1) social, ethnicity, and geographic difference can differ the prevalence of *H. pylori* infection in human; 2) as mentioned before, not only the infection itself gives the risk for gastric malignancies, but many other factors contribute to give the outcome of gastric cancer and gastric lymphoma. Last but not least, prevalence can vary by using difference diagnostic methods or definition (serology, culture, and histopathology), make us tobe very careful when broadcasting epidemiologic data of *H. pylori* infection.[12]

Prevalence of *H. pylori* infection worldwidely varies from 13 to 92% due to where the study was conducted.[6] Developing countries suffer more from this infection than the developed one.[16] Africa and East Asian has the highest prevalence while American and European countries has low prevalence. It is resumed that level of education and socio-economic stratification strongly correlated with the infection.[6,7,17]

By serological methods, there is a decrease of prevalence of *H. pylori* infection worldwide. From nationalpopulation studies in East Asian countries, such as Japan, Korea, Taiwan, and Indonesia, the seroprevalence of *H. pylori* has decreased in the last ten years. These separated studies has been concluded in Asia Pacific Consensus Guideline for *Helicobacter pylori* infection that the prevalence of the infection has been declining in the region.[5] This epidemiology phenomenon was due to the successful screening program and treatment of the infection globally. As the burden decreased, the risk of peptic ulcers and gastric cancer in numerous countries has also been reduced. However, not all areas are the same. In Indonesia, there was decreased prevalence of *H. pylori* infection in 8 year-period but there was no decreased prevalence of intestinal metaplasia and gastric cancer.[9]

Despite the decrease of the prevalence worldwidely, there are some issues of therapy failure in several studies.[18,19] This is caused by resistance of some strains to antimicrobial, especially metronidazole and clarythromycin, in some populations. Generally, the resistance rate to clarythromycin is 17.2%, while metronidazole 26.7%, amoxicillin 11.2%, levofloxacin 1.2%, and combination of antibiotics 9.6% rate of resistancy.[20]

Decrease of successful rate and increase prevalence of *H. pylori* resistant strains make treatment of *H. pylori* infection still challenging.[21] At a glance, it is contradictive with the burden reduction in developed countries. However, if we stratify the resistance problems, we can see that this majority happened in developing countries. It is strongly recommended that study and program of eradication and solution of resistance problemsare directed in specific population.[22] It will save a lot of study fund.

Selective populations in the same geographic area also have difference prevalence of *H. pylori* infection. Study by den Hollander et al revealed that despite of the declining of *H. pylori* infection in developed countries, the immigrants in these countries have higher number of prevalence, contributed to the actual epidemiology data in the region.[23] The study in multi-ethnic European city gave a big deviation between Dutch versus non-Ducth *H. pylori* infection prevalence (24% vs. 64%). This phenomenon is very important for public health programs, that screening and eradication programs not always similar for all of the population in one country, but must be selected in sub-population. This is also due to the variation of strains of *H. pylori* found in specific population or ethnicity worldwidely.[14]

It has been concluded from many studies that infection of *H. pylori* has strong (causality) link with gastric cancer.[11] However, there are notable paradoxical epidemiology phenomenon that in some region, high prevalence of *H. pylori* infection is not followed by high incidence of gastric cancer. Africa has the highest prevalence of *H. pylori* infection but very low incidence of gastric cancer. The same phenomenon happen in India. Goh et al studied about this phenomenon in his country which has three major ethnicity; Indian, Chinese, and Malay decent.[22] The study revealed that among the three ethnicity, Indian decent has the highest prevalence of *H. pylori* infection, but low incidence of gastric cancer, while Malay decent has either low prevalence of infection and also low incidence of gastric cancer.[22,24]

Many reviews hypothesize that trias Gordon, interaction between host, bacterial, and environment, strongly occur in the event of gastric cancer and its correlation with *H. pylori* infection. From the prespective of the bacteria, virulence factors of CagA with East Asian type (EPIYA-D) present in

Chinese population, while Western type (EPIYA-C) predominantly occur in Indian population.[25,26] *H. pylori* also interacts with hosts who are susceptible to have chronic inflammation, atrophy of gastric mucosa, and development of cancer. Finally, many factors interact in the event of gastric cancer. Shortly, in epidemiology terminology, helicobacter infection is asufficient factor for gastric cancer.

CURRENT CLINICAL ISSUES OF *HELICOBACTER PYLORI* INFECTION

There are three guidelines which are used globally to manage *H. pylori* infection; Maastricht IV/Florence Consensus, American College of Gastroenterology (ACG) Guideline on the Management of *H. pylori* infection, and Second Asia-Pacific Consensus Guidelines for *H. pylori* infection.[2,5,27,28] National guidelines such as Brazilian and Indonesian adapted these established guidelines. These three guidelines are a must read consensus for all clinicians treating *H. pylori* infection patient.[29,30]Among them, the ACG Guideline, which published in American Journal of Gastroenterology, remains the eldest consensus, but still relevant for clinicians all over the world. Maastricht IV/Florence Consensus was first published in 2010, and was republished in *Gut* in 2012.[27] For Asian countries where the prevalence of *H. pylori* is high, they can alsouse the Second Asia-Pacific Consensus Guidelines for *H. pylori* infection. The consensus conference was held in 2008 in Bangkok. The guidelines was first published in Journal of Gastroenterology and Hepatology in 2009.[5]

The basic principles to test and treat *H. pylori* from the three consensus was relatively the same. From these guidelines, a test-and-treat strategy is appropriate for uninvestigated dyspepsia inpopulations where the *H. pylori* prevalence is high (> 20%). This approach is subject to patients with alarming symptoms or older patients (high risk for cancer). It should be kept in mind that main non-invasive tests that can be used for the test-and-treat strategy are the urea breath test (UBT) and monoclonal stool antigen tests. Certain validated serological tests can also be used. UBT and monoclonal stool antigen tests is also the appropriate test to confirm the eradication of *H. pylori* infection. The diagnostic test of *H. pylori* can only be performed if there is a plan to offer a treatment for positive results.[26]

Indications for treating *H. pylori* infection are also the same in these three guidelines; peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma (MALToma), atrophic gastritis, history of gastric cancer resection, history of gastric cancer in the family, patient's wishes, non-ulcer dyspepsia, before starting long-term aspirin therapy for high risk for ulcer patients, gastroesophageal reflux disease (GERD) requiring long-term proton pump inhibitor, and community prevention for gastric cancer in the region with high incidence of gastric cancer.[5] In ACG guideline, there is a separation of established and controversial indication for diagnostic and treatment of *H. pylori* infection, with the controversial indications are persons using non-steroidal anti-inflammatory drugs (NSAIDs), unexplained iron deficiency anemia, GERD, and non-ulcer dyspepsia.[2]

Based on ACG guideline on the management of *H. pylori*, first-line regimens for *H. pylori* eradication are standard dose of proton pump inhibitor (PPI) twice daily, clarythromycin 500 mg twice daily, and amoxicillin 1,000 mg twice daily (duration 10-14 days), or standard dose PPI twice daily, clarythromicyn 500 mg twice daily, and metronidazole 500 mg twice daily (duration 10-14 days), or bismuth subsalicylate 525 mg fourth daily, metronidazole 250 mg fourth daily, tetracycline 500 mg fourth daily, and standard dose PPI fourth to twice daily (duration 10-14 days), or PPI + amoxicillin 1000 mg twice daily (for 5 days) followed by PPI, clarythromycin 500 mg, and tinidazole 500 mg twice daily (for 5 days).[2] In second Asia Pacific Consensus Guideline for *H. pylori* Infection, triple therapy with clarythromycin and amoxicillin for 7 days is the choice among several first-line regimens. The slight difference with the ACG guideline of the management of *Helicobacter pylori* is the duration of the therapy, which is 7-14 days according to the Asian Pacific Consensus for *Helicobacter pylori* Infection.[5] For clinicians, we must consider the therapy duration with cost-benefit analysis.

From meta-analysis studies from global population, it is stated that a 10-day treatment improves the eradication rate by 4% and a 14-day treatment improves the eradication rate by 5-6%, in comparison to a 7-day treatment. However, for the single Asian study in the meta-analysis that compared 14- with 7-day treatment, there was no difference in *H. pylori* eradication rates.[21] It is concluded in the guideline that there is only minor statistical differences between 14- and 7-day treatment and the choice for duration requires cost-effective and compliance considering decision.[5]

Resistance issue is a bad news in the success story of declining prevalence of *H. pylori* infection worldwide.[18-20] Although the prevalence is also reduced,

Asian countries have the highest burden of resistancy compared to Western countries.[5] Clarythromycin and metronidazole are the two antimicrobials that faced the highest resistancy issue. This phenomenon reduced the efficacy of PPI-based triple therapy. There are insufficient data to recommend sequential therapy as an alternativeto first-line therapy in Asia. Salvage therapy for the infection include; (a) standard triple therapy that has not been previously used; (b) bismuth-based quadruple therapy; (c) levofloxacin-based triple therapy; (d) rifabutin-based triple therapy. Agreed with Asian statement, ACG also stated that there are no adequate evidences to support which salvage therapy is better than the others. Since patients usually get triple therapy with clarythromycin as previous treatment, the treatment of choice for salvage therapy is bismuth-quadruple therapy containing tetracycline and metronidazole.[5]

Another highlight in the therapy of *H. pylori* infection is the use of probiotics to improve eradication.[31-33] In these three guidelines, only Maasctrich consensus stated about the use of probiotics with the recommendation D (expert opinion without explicit critical appraisal or based on physiology, bench research or 'first principles'), while ACG and Asia Pacific guideline did not mention about probiotics at all.[26] The consensus stated thatcertain probiotics and prebiotics show promising results as an adjuvant treatment in reducing side effects.

Abdullah et al stated that there are four protective mechanisms of probiotics in the context of *H. pylori* infection, which are producing antimicrobial substance, stabilizing the mucosal barier of the stomach, preventing adhesion of *H. pylori*, and modifying host immune responses. SCFAs and bacteriocin produced by probiotics impair the growth of bacteria. Probiotics also inhibit the colonization of *H. pylori*, and reduce tumor necrosis factor and interleukin-8 which act as the pro-inflammatory cytokines.[34]

Lactoferrin and *Lactobacilli* are two probiotics which often used in several trial to increase successful rate of *Helicobacter pylori* eradication treatment.[27,32,33] From the study done by Lesbros-Pantoflickova et al, long-term intake of products containing probiotic strains may have a favorable effect on *H. pylori* infection in humans, particularly by reducing the risk of developing disorders associated with high degrees of gastric inflammation.[35] Recently, two meta-analyses support the evidence of adding probiotics in the regimens can increase the efficacy of PPI-clarythromycin containing triple therapy. However, lack quality control of the trials need clarification from other studies in the future.[26]

CONCLUSION

Before 1980s, no one could ever think about species which could live in human gaster. For the study which led on behalf public health, we are now celebrating 30 years discovery of *H. pylori* by Barry Marshall and Robbin Warren. Many studies, methods, and developments have been made in the last thirty years, but the escalation happened in the last ten years. There are some strategies made by the bacteria to 'keep safe' in human stomach, but at the same time, it develops higher virulence factors to human body. Epidemiology study always beneficial for the community and molecular mapping of the infection, along with the beneficial impacts of treatment program, resistancy issues, and eradication monitoring. Last but not least, the comparison of three most influential guidelines used to manage *H. pylori* clinically need to be understood, and as a clinician, we must adopt these statements carefully, with the clinical critical thinking. Use of probiotics is the latest hot issue now. We can predict in the future guidelines, probiotics will be given bigger portion since the molecular and clinical evidences supporting its benefit growing unstoppable.

CONFLICT OF INTEREST

We hereby declare that we have no conflict of interest with anyone in writing this article.

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