Gut Microbiota for Integrative Wellness

EDITORIAL

Helicobacter pylori interpretation in 2022

Alfred Chin Yen Tay[1,*], Barry James Marshall[1,2,3]

[1]The Marshall Centre for Infectious Diseases, Research and Training, University of Western Australia, Perth 6009, WA, Australia
[2]Marshall Laboratory of Biomedical Engineering, School of Biomedical Engineering, Shenzhen University Health Science Center, Shenzhen 518060, Guangdong Province, China
[3]Marshall International Digestive Diseases Hospital, Zhengzhou University, Zhengzhou 450001, Zhengzhou Province, China

Helicobacter pylori, or formally known as *Campylobacter pylori*, is a Gram negative, micro-aerophilic, spiral microorganism that can colonise the healthy stomach lining. It is associated with gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer.[1–3] At least 50% of the world population is still infected with *H. pylori* and about 1 million new gastric cancer cases are reported annually.[4] In 1994 and 2017, the WHO classified *H. pylori* as a Class I carcinogen[5,6] and listed it as one of the most important (priority high) pathogens for emerging antibiotic resistance alarm,[7,8] respectively.

It is interesting that 40 years after its discovery, with tens of thousands of research articles published, the route of transmission and the mechanism of how *H. pylori* causes cancer remains unclear. We now know that *H. pylori* survives poorly outside the human body. *In vitro*, *H. pylori* is known to be sensitive to heat, salt, chilli, honey, and many other common food ingredients.[9] This has made it difficult to transmit to other individuals *via* food sharing. However, people living under the same roof, with daily close contact, have been shown to infect each other.[10] On the flip side, we have also observed couples with good oral hygiene that have lived together for decades but have not infected each other. Perhaps a simple step in taking care of oral hygiene is sufficient in stopping *H. pylori* transmission.

The consensus is that we predominantly acquire *H. pylori* during childhood, perhaps *via* the oral-oral route, and traditionally from an infected mother to child. For example, it is common practice in certain region that a mother would use her mouth to test the temperature of the food and even pre-masticate to break the food into smaller pieces before feeding to her child. Whereas, in modern society, an infected father who shares the feeding duties could also be the source of infection. In situations where both parents must work, the caring duty may be given to either the grand-parents or nanny, who may be infected. Nevertheless, there is strong evidence to suggest that, as social economic status is improved, the prevalence of *H. pylori* declines.[11–13]

Australia is one of the few countries that have a low prevalence of *H. pylori* (about 15%). However, the prevalence of *H. pylori* among the Aboriginal and the Asian communities can be as high as 50%–80%.[14,15] We believe that the overall low prevalence of *H. pylori* is the major factor for the low gastric cancer incidence in Australia (7.3 cases per 100,000 persons 10 for males and 4.5 for females).[16] Gastric cancer may no longer be an Australian problem, but it is still the 5th top cancer-killer in the world.[4,17] Interestingly, about 50% of the newly reported gastric cancers are concentrated in the Eastern Asia countries, such as Japan, Korea, Mongolia and China.[4] Furthermore, all these Eastern Asia countries are dominated by the hpEAsia strain.[18,19] Cytotoxin-associated gene A (CagA) is arguably the most studied virulence factor of *H. pylori*. It is encoded on the 40kb cag pathogenicity island and it is the only known effector protein to be injected into host cells.[20] There are two types of CagA protein, the Western type (EPIYA-ABC) and the Eastern type (EPIYA-ABD). Not every type of *H. pylori* carries CagA toxin. However, almost all hpEAsia type carries the more toxigenic Eastern CagA. CagA can lead to inflammation,[21] affecting the survival of B cells[22] and changes the

***Corresponding Author:**
Alfred Chin Yen Tay, The Marshall Centre for Infectious Diseases, Research and Training, University of Western Australia, 35 Stirling Highway, Crawley, Perth 6009, WA, Australia. Email: alfred.tay@uwa.edu.au. https://orcid.org/0000-0001-9705-4010
Received: 29 April 2022; Revised: 30 May 2023; Accepted: 8 June 2023; Published: 16 June 2023
https://doi.org/10.54844/gmiw.2022.0089

histological characteristics of the stomach.[23] The Eastern CagA is probably one of the major factors contributing to gastric cancer.

Presently, there is no standard treatment guideline for patients who carry antibiotic resistant *H. pylori* strains. Without the proper testing of antibiotic resistance in the laboratory, doctors are relying on experience and experimenting with different antibiotic combinations. This strategy may work for now, but we fear that it will only promote stronger antibiotic resistance in the future.

Thus, the best strategy for dealing with patients who failed multiple antibiotic treatment is to provide antibiotic susceptibility testing. Such personalised precision medicine has been proven to have high success rate. However, this strategy faces two challenges: 1. How to obtain *H. pylori* from the patients; 2. How to culture *H. pylori* and diagnose for antibiotic resistance. The traditional method of obtaining *H. pylori* is by performing endoscopy. This has caused some difficulties for some individuals. Other than the expensive cost of the procedure, many remote hospitals are not equipped with endoscopy suite. Alternative technologies, such as the String Test that does not require medical specialists, should be investigated. Such technology doesn't require a lot of skill and can be done anywhere. String Test can also help patients who recently had endoscopy examination done to avoid another one just to obtain the *H. pylori* specimen.

In regard to *H. pylori* culture. Not only that it is laborious, it also requires skill and a lot of time. Usually, it would require at least 2–3 weeks to process from biopsy to antibiotic resistance report. As a result, not many laboratories are capable of culturing such a fastidious microorganism.[24–26] Nevertheless, as the molecular technology is getting advance, a robust and sensitive qPCR method to obtain antibiotic resistance diagnosis within a day may be the alternative path overcoming the culturing hurdle. But qPCR is only accurate on clarithromycin and quinolones resistance at the moment. The antibiotic resistance mechanisms for other antibiotics are not fully understood. Some may involve multiple single-nucleotide polymorphism (SNP) of different genes. As a result, qPCR is still not accurate in detecting resistance from amoxicillin, metronidazole, rifabutin, tetracycline and furazolidone. Hopefully in a not very distant future, we will be able to use the big data analysis and artificial intelligent to help us solve this issue.

While the success rate of the standard *H. pylori* triple therapy (PPI + Amoxicillin + Metronidazole/ Clarithromycin) is declining globally, and is even abandoned in some countries, it remains effective in Australia.[15] Nevertheless, for those who failed the standard triple therapy, the alternative antibiotics used in rescue regimens include quinolones, rifampicin, tetracycline and furazolidone. While quinolones and rifampicin are effective antibiotics against *H. pylori*, the organism can be easily become resistant to these as well. Therefore, a better strategy in choosing antibiotic combination is required. To date, we still hear stories about patients who failed multiple times on the same treatment. It is important to remind doctors not to prescribe the same antibiotic combination to the patient who failed the *H. pylori* treatment, as the *H. pylori* must have already gained resistance to the treatment. Then again, resistance to bismuth, amoxicillin, tetracycline, and furazolidone are very rare. It is true that we come across reports of amoxicillin resistance from time to time. However, because it is so rare, and resuscitation from deep freezer can sometimes revert its resistance, this showed that we are still not clear of the mechanism of its resistance and hence, uncertain the reliability of such report. Bismuth on the other hand, have been used in medicine for over three centuries and were first introduced to treat duodenal ulcer in 1987,[27] it cannot be absorbed by human body. However, bismuth can give very dark stool and be mistaken for internal bleeding. Because of that, its usage was once prohibited by many countries. Then again, due to the gradual increase of antibiotic resistance, bismuth is once again be considered for *H. pylori* treatment. Most importantly, bismuth can prevent *C. diff* complication from using antibiotics. Not only that there are reports about overcoming metronidazole resistance by combination with tetracycline, but simply adding bismuth to triple therapy for 14 days has been reported to have an efficacy of more than 90%.[28] Finally, as a reminder, other than non-compliance, antibiotic resistance is the primary reason for treatment failure. Therefore, for patients who failed a quadruple therapy, please do not prescribe the same antibiotic combination in a short period of time.

For many antibiotic treatments, the key factor to the success is the concurrent use of a high-dose Proton Pump Inhibitor (PPI). It is already known that the use of antibiotics alone is not enough to eradicate *H. pylori*. Acid reduction therefore plays a vital role in *H. pylori* treatment. To elaborate on this, the reader should note that most antibiotics were developed without the gastric mucosa in mind. Therefore, they might not act in the gastrointestinal lumen, and especially not in an acid environment. Interestingly, metronidazole and clarithromycin, which are secreted in saliva, are particularly effective against naïve *H. pylori* strains, perhaps for this reason. Bismuth compound acts topically on the gastric mucosa and is safe and effective (used for at least 200 years for gastrointestinal disorders). However, bismuth does not penetrate the mucus layer so always needs an extra antibiotic agent to provide a permanent cure.

Regarding acid lowering agents, one aims to achieve round the clock pH ≥ 6 in the stomach. H_2 blockers (cimetidine "Tagamet", ranitidine "Zantac", famotidine "Calmicidetc", and *etc.*) are competitive inhibitors of acid secretion so cannot reliably do this. The PPI drugs were a breakthrough in this regard (omeprazole "Losec", esomeprazole "Nexium", rabeprazole "Aciphex", and *etc.*) almost completely blocking the proton pumps. However, some *H. pylori* could survive, perhaps reflecting an inadequate dose in some patients.

Recently, the potassium competitive acid blocker group (P-CABs) has been used (Vonoprazan) in Japan which might give a rapid and more complete acid blockade, with subsequent excellent cure rate for *H. pylori*. Perhaps even with just a single antibiotic such as amoxicillin. Time will tell.

But the controversy still rages, "should we give treatment to asymptomatic *H. pylori* carriers?" Asymptomatic patients with a family history of gastric cancer, or with gastric intestinal metaplasia, or atrophic gastritis, are advised to get rid of their *H. pylori*. In regions with high prevalence of gastric cancer, such as Eastern Asia, where the "cancer strain" of *H. pylori* predominates, should all be encouraged to eradicate the *H. pylori* infection? The risk of getting gastric cancer increases with age. Since most people acquire *H. pylori* during childhood and assuming that the damage of the gastric mucosa accumulates through age, the chance of developing gastric cancer increases. Perhaps because the seeds of cancer have already been planted, getting rid of *H. pylori* in old age does not always eliminate the gastric cancer risk. However, it has been reported that in all age groups, patients with a history of *H. pylori* infection have a higher risk of gastric cancer than those that have never been infected.[29–31]

So other than antibiotics, is there no other natural products than be used to treat *H. pylori* infection? In the laboratory, many spices, food ingredients such as salt, sugar, vinegar, chilli, pepper, garlic, ginger, honey and others were shown to have inhibitory effect on *H. pylori*.[24,32–34] However, these products are useless against *H. pylori* when ingested by human. This is because *H. pylori* only colonises the internal gastric luminal surfaces, albeit under the mucus layer. While the mucus protects the stomach epithelial cells by blocking the acid from destroying them, it also blocks the ingested food from reaching the bacteria. Besides, the strong stomach acid is probably going to destroy anything that has anti-microbial effect on *H. pylori*. As for antibiotics, they were absorbed by the body and were delivered to every cells in the whole body. When *H. pylori* is extracting nutrients from the gastric cells, antibiotics can then kill the bacteria. That is why it is common that after you have taken some antibiotics, you can sometimes taste the bitterness in the mouth. That is because the absorbed antibiotics are secreted in your saliva and constantly feed into your stomach. As a result, the natural products may be helpful in treating the symptoms but have zero effect on *H. pylori* infection. Nevertheless, most natural products (including probiotics) are generally regard as safe. These natural products may be helpful in replenishing the microbiota after strong antibiotics treatment. Therefore, we are not against people from taking them.

In summary then, susceptibility guided precision medicine is the way forward for eradication of *H. pylori*. New combination therapies show promise and the dream of 100% cure of the infection with minimal side effects from treatment seems achievable. The next decade will see combination therapies with newer acid blockers in widespread use at reasonable cost. Investment in new antibiotics and strategies to combat the rise of antibiotic resistant microorganisms is vital. The famous quote by David Graham "The only good *H. pylori* is a dead *H. pylori*"[35] seems the way to go.

DECLARATION

Conflict of interest

Barry James Marshall is the co-founder for Shenzhen Hongmed-Infagen Co. Ltd. which provides the string-qPCR testing service in this Editorial. Alfred Chin Yen Tay is the honorary co-founder for Shenzhen Hongmed-Infagen Co. Ltd. which provides the string-qPCR testing service in this Editorial.

REFERENCES

1. Labigne A, de Reuse H. Determinants of Helicobacter pylori pathogenicity. *Infect Agents Dis*. 1996;5(4):191–202.
2. McColl KE. Helicobacter pylori: clinical aspects. *J Infect*. 1997;34(1):7–13.
3. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*. 1984;1(8390):1311–1315.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018:GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
5. Working Group on the Evaluation of Carcinogenic Risks to Humans. Schistosomes, liver flukes and Helicobacter pylori. *IARC Monogr Eval Carcinog Risks Hum*. 1994;61:1–241.
6. Moss SF. The clinical evidence linking Helicobacter pylori to gastric cancer. *Cell Mol Gastroenterol Hepatol*. 2017;3(2):183–191.
7. Tacconelli E, Carrara E, Savoldi A, *et al*. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. 2018;18(3):318–327.
8. Dang BN, Graham DY. Helicobacter pylori infection and antibiotic resistance: a WHO high priority? *Nat Rev Gastroenterol Hepatol*. 2017;14(7):383–384.
9. O'Mahony R, Al-Khtheeri H, Weerasekera D, *et al*. Bactericidal and anti-adhesive properties of culinary and medicinal plants against Helicobacter pylori. *World J Gastroenterol*. 2005;11(47):7499–7507.

10. Sari YS, Can D, Tunali V, Sahin O, Koc O, Bender O. H pylori: treatment for the patient only or the whole family? *World J Gastroenterol*. 2008;14(8):1244–127.
11. Elshair M, Ugai T, Oze I, *et al*. Impact of socioeconomic status and sibling number on the prevalence of Helicobacter pylori infection: a cross-sectional study in a Japanese population. *Nagoya J Med Sci*. 2022;84(2):374–387.
12. Genta RM, Turner KO, Sonnenberg A. Demographic and socioeconomic influences on Helicobacter pylori gastritis and its pre-neoplastic lesions amongst US residents. A. *liment Pharmacol Ther*. 2017;46(3):322–330.
13. Malfertheiner P, Camargo MC, El-Omar E, *et al*. Helicobacter pylori infection. *Nat Rev Dis Primers*. 2023;9(1):19.
14. Windsor HM, Abioye-Kuteyi EA, Leber JM, Morrow SD, Bulsara MK, Marshall BJ. Prevalence of Helicobacter pylori in Indigenous Western Australians: comparison between urban and remote rural populations. *Med J Aust*. 2005;182(5):210–213.
15. Wise MJ, Lamichhane B, Webberley KM. A longitudinal, population-level, big-data study of Helicobacter pylori-related disease across western Australia. *J Clin Med*. 2019;8(11):1821.
16. Australian Institute of Health and Welfare. Stomach cancer statistics. Accessed March, 23 2021. https://www.wcrf.org/cancer-trends/stomach-cancer-statistics
17. Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020:GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249.
18. Higashi H, Tsutsumi R, Fujita A, *et al*. Biological activity of the Helicobacter pylori virulence factor CagA is determined by variation in the tyrosine phosphorylation sites. *Proc Natl Acad Sci U S A*. 2002;99(22):14428–14433.
19. Olbermann P, Josenhans C, Moodley Y, *et al*. A global overview of the genetic and functional diversity in the Helicobacter pylori cag pathogenicity island. *PLoS Genet*. 2010;6(8):e1001069.
20. Censini S, Lange C, Xiang Z, *et al*. Cag, a pathogenicity island of Helicobacter pylori, encodes type I-specific and disease-associated virulence factors. *Proc Natl Acad Sci U S A*. 1996;93(25):14648–14653.
21. Posselt G, Backert S, Wessler S. The functional interplay of Helicobacter pylori factors with gastric epithelial cells induces a multi-step process in pathogenesis. *Cell Commun Signal*. 2013;11:77.
22. Umehara S, Higashi H, Ohnishi N, Asaka M, Hatakeyama M. Effects of Helicobacter pylori CagA protein on the growth and survival of B lymphocytes, the origin of MALT lymphoma. *Oncogene*. 2003;22(51):8337–8342.
23. Murata-Kamiya N, Kurashima Y, Teishikata Y, *et al*. Helicobacter pylori CagA interacts with E-cadherin and deregulates the beta-catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. *Oncogene*. 2007;26(32):4617–4626.
24. Allison R, Lecky DM, Bull M, Turner K, Godbole G, McNulty CAM. Audit of Helicobacter pylori testing in microbiology laboratories in England: to inform compliance with NICE guidance and the feasibility of routine antimicrobial resistance surveillance. *Int J Microbiol*. 2016;2016:8540904.
25. Llorca-Otero L, Toro-Rueda C. Diagnosis of Helicobacter pylori infection: progress and challenges. *Enferm Infecc Microbiol Clin (Engl Ed)*. 2020;38(9):407–409.
26. Zullo A, Francesco V, Gatta L. Helicobacter pylori culture: from bench to bedside. Ann. *Gastroenterol*. 2022;35(3):243–248.
27. Marshall BJ, Armstrong JA, Francis GJ, Nokes NT, Wee SH. Antibacterial action of bismuth in relation to Campylobacter pyloridis colonization and gastritis. *Digestion*. 1987;37 Suppl 2:16–30.
28. McNicholl AG, Bordin DS, Lucendo A, *et al*. Combination of bismuth and standard triple therapy eradicates Helicobacter pylori infection in more than 90% of patients. *Clin Gastroenterol Hepatol*. 2020;18(1):89–98.
29. Kumar S, Metz DC, Ellenberg S, Kaplan DE, Goldberg DS. Risk factors and incidence of gastric cancer after detection of Helicobacter pylori infection: a large cohort study. *Gastroenterology*. 2020;158(3):527–536.e7.
30. Leung WK, Wong IOL, Cheung KS, *et al*. Effects of Helicobacter pylori treatment on incidence of gastric cancer in older individuals. *Gastroenterology*. 2018;155(1):67–75.
31. Choi IJ, Kim CG, Lee JY, *et al*. Family history of gastric cancer and Helicobacter pylori treatment. *N Engl J Med*. 2020;382(5):427–436.
32. Fahey JW, Stephenson KK, Wallace AJ. Dietary amelioration of Helicobacter infection. *Nutr Res*. 2015;35(6):461–473.
33. Graham DY, Anderson SY, Lang T. Garlic or jalapeño peppers for treatment of Helicobacter pylori infection. *Am J Gastroenterol*. 1999;94(5):1200–1202.
34. O'Mahony R, Al-Khtheeri H, Weerasekera D, *et al*. Bactericidal and anti-adhesive properties of culinary and medicinal plants against Helicobacter pylori. *World J Gastroenterol*. 2005;11(47):7499–7507.
35. Graham DY. The only good Helicobacter pylori is a dead Helicobacter pylori. *Lancet*. 1997;350 (9070):70–71.