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Perspective

PERSPECTIVE

Helicobacter pylori infection is an infectious disease and the empiric therapy paradigm should be changed

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Abstract

Helicobacter pylori infection is an infectious disease. Given the alarmingly high antibiotic resistance in *H. pylori*, gastroenterologists should change the empiric *H. pylori* treatment paradigm to an antimicrobial susceptibility testing-guided precision treatment. Antimicrobial stewardship programs for *H. pylori* should be implemented locally, regionally, and nationally to monitor the antibiotic resistance pattern.

Key words: *Helicobacter pylori*; antimicrobial susceptibility testing; infectious disease

Helicobacter pylori is the only bacterium classified as a Group I carcinogen

Helicobacter pylori is a human gastric pathogen that has infected more than half of the world's population.[1] In the absence of antibiotic treatment, the infection causes chronic active gastritis, and from this, 15%–20% of patients will develop peptic ulcers and approximately 1%–3% will ultimately develop gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma.[2] It is now established that chronic *H. pylori* infection is the most important etiological factor for gastric cancer,[2–5] the third leading cause of cancer death globally.[6] Approximately 89% of worldwide gastric cancer cases are attributable to chronic *H. pylori* infection.[6] In 1994, the WHO International Agency for Research on Cancer (IARC) classified *H. pylori* as a Group I carcinogen. *H. pylori* eradication has now been recommended as the primary strategy for preventing gastric cancer in all recently developed guidelines.[2–5,7,8]

Empiric treatment of *H. pylori* has contributed to misuse and overuse of antibiotics

Because of the difficulty in culturing *H. pylori* in the laboratory and the long waiting time for antibiotic susceptibility

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testing results, empiric treatment has always been the recommended strategy for *H. pylori* infection.[2–5,7,8] When the antibiotic resistance rate is low, empiric triple therapy consisting of a proton pump inhibitor (PPI) plus two antibiotics (amoxicillin with clarithromycin or metronidazole) can be used to achieve a satisfactory cure rate. However, as the antibiotic resistance rate rises, the success rate of empiric triple therapy in many countries has fallen to an unacceptably low level (<60%).[9–11] Antibiotic resistance is the major cause of treatment failure and is responsible for the declining rates of *H. pylori* eradication reported in many countries. In Europe, conventional triple therapy has already been abandoned and replaced by quadruple therapy.[2,4,5] However, because there is no guideline for quadruple therapy, "random" antibiotic combinations have been proposed and tried globally, especially in regions where antibiotic resistance rate is high. From what we can see to date, such a strategy has already led to a gradual increase of quinolone and rifabutin resistance.

The recent international *H. pylori* treatment guidelines recommend the use of empiric concomitant quadruple therapy consisting of a PPI plus three antibiotics (amoxicillin, clarithromycin, and metronidazole) administered concurrently to overcome *H. pylori* antibiotic resistance.[2,4,7] The rationale behind the empiric concomitant quadruple therapy is not evidence-based but "hope-based", and therefore it is nicknamed "hope therapy" because gastroenterologists hoped that the infection would be susceptible to either clarithromycin or metronidazole.[12,13] Unfortunately, our experience is that many patients infected with *H. pylori* in whom treatment has failed, have concurrent dual resistance to clarithromycin and metronidazole, or even triple resistance to clarithromycin, metronidazole, and fluoroquinolone (using culture-based antimicrobial susceptibility testing). As a result of misuse of antibiotics, concomitant quadruple therapy is rapidly losing its efficacy.

In regions with a high resistance rate to clarithromycin and metronidazole (>15%), bismuth-based quadruple therapy consisting of a PPI, bismuth, tetracycline, and metronidazole, is the recommended replacement for concomitant quadruple therapy.[2,4,7] It is noted that not only that *H. pylori* can never become resistant to bismuth salts, but more importantly, the use of bismuth may prevent complications from *Clostridium difficile*.[14,15] The Fifth Chinese National *H. pylori* Consensus recommended seven bismuth-based quadruple regimens with different combinations of two other antibiotics (amoxicillin, clarithromycin, metronidazole, levofloxacin, tetracycline, and furazolidone).[5] Although the Consensus guideline recommended that the choice of regimens should be based on the local *H. pylori* antibiotic resistance profile,[5] in reality, such a profile is unavailable in many regional areas. Moreover, modern transport systems have allowed mass migration of the human population in a short period of time. Without a proper guideline for the choice of antibiotics for subsequent rescue therapy, it is not practical to guesstimate the antibiotic resistance profile.

H. pylori infection is an infectious disease and should be treated like one

Since the 2015 Kyoto *H. pylori* consensus, *H. pylori* infection has been defined as an infectious disease regardless of clinical symptoms and complications.[2–5,8] This serves as a start to shift our thinking to the appropriate use of antibiotics for treating *H. pylori* infection. The Maastricht V Consensus recommended that after failure of a second-line strategy, *H. pylori* treatment should be guided by antimicrobial susceptibility testing.[2] Nevertheless, in the face of rampant antibiotic resistance, it would be wiser to routinely perform antimicrobial susceptibility testing, if an endoscopy is carried out, to tailor the treatment from the very beginning. The optimal age threshold for endoscopy screening has been lowered to 35 years old in Asian countries with high incidence of gastric cancer.[5,16] In China, the cost of endoscopy is low (approximately 100 U.S. dollars) and it is widely applied as the first screening choice (depending on the patient's willingness) to reduce the risk of missing the diagnosis of upper gastrointestinal cancer.[5]

Many clinicians argue that antimicrobial susceptibility testing is laborious and time-consuming, while the truth is that *H. pylori* can be cultured in almost every microbiology laboratory if the relevant training is provided to the microbiologists, so that they can provide the susceptibility testing to guide the treatment of *H. pylori*. However, asking every hospital to provide antimicrobial susceptibility testing would not be cost-effective. With ever-improving medical express delivery services, it would be wiser to outsource the culture and antimicrobial susceptibility testing to professional third-party independent *H. pylori* labs. Culture of *H. pylori* and subsequent susceptibility testing take 1–2 weeks, and indeed are time-consuming; however, there is no rush to initiate the treatment without knowing the susceptibility testing results because most of the patients have had the infection for decades (*H. pylori* is usually acquired in childhood).[4] Thus, waiting 1–2 weeks does not do any harm to the patients, but offers an opportunity for "treating it right the first time". This is very important as the cure rate is highest with initial therapy if the right antibiotics are chosen, whereas after failure of initial therapy, the bacterium will mostly likely develop drug resistance and it will become more difficult to treat.

How to achieve excellent *H. pylori* treatment success (≥95% cure rate): the devil is in the detail

In addition to choosing the right antibiotics based on antimicrobial susceptibility testing, potent gastric acid inhibition is an important factor influencing treatment success. Thus, selecting a PPI with higher acid-inhibitory potency and less influence from host CYP2C19 polymorphisms (rabeprazole, esomeprazole, and ilaprazole) can improve the cure rate.[2] The Maastricht V Consensus states that

the use of high-dose PPI controls the gastric pH more adequately, thus increasing the therapy efficacy.[2] Of note, as the acid-inhibitory potency of different PPIs varies markedly, simply doubling the standard dose of any PPI provides dramatically different effects.[17] For example, doubling the standard dose of esomeprazole from 20 mg to 40 mg equals the effect of 64 mg omeprazole; while doubling the standard dose of rabeprazole from 20 mg to 40 mg equals the effect of 74 mg omeprazole.[17] The standard dose of pantoprazole of 40 mg is only equivalent to 9 mg omeprazole, and therefore pantoprazole is no longer recommended.[13,17] Many physicians are afraid of prescribing a double dose of PPIs because of concerns regarding increased side effects. However, PPIs are remarkably safe and serious adverse effects are extremely rare. Then the only cause for concern is the doubled cost rather than reduced safety from doubling the PPI dose. The new PPI (vonoprazan), a potassium-competitive acid blocker recently approved for *H. pylori* eradication in Japan, exerts a more potent acid-inhibitory effect than current PPIs and is unaffected by host CYP2C19 polymorphisms and meals,[18] and thus is likely to be used widely in future anti-*H. pylori* regimens.

Patient's compliance is another key factor for successful treatment. Treatment of *H. pylori* with a combination of two or three antibiotics can have apparent side effects including abdominal pain, headache, dizziness, nausea, vomiting, and rash, resulting in poor compliance, especially in patients taking the classic bismuth quadruple regimen with antibiotic combination of tetracycline and metronidazole, or the extended regimen with combination of tetracycline and furazolidone. However, most of these side effects are tolerable or avoidable if clinicians can take time to emphasize the importance of adhering to treatment regimens for a full course of 10–14 days, and instruct their patients on timing of doses in relation to meals (administer PPI and bismuth 30 minutes before meals, whereas take the antibiotics 30 minutes after meals), and the avoidance of alcohol taken with metronidazole, and avoidance of all cheeses, soybeans and soy sauce taken with furazolidone.[19]

In summary, *H. pylori* infection is an infectious disease and excellent treatment success (≥95% cure rate) can be achieved with well-designed regimens based on the individualized (or precision) choice of antibiotics coming from culture and antimicrobial susceptibility testing, the right choice and doses of PPIs, the inclusion of bismuth (if available), and good patients' compliance. Given the alarmingly high antibiotic resistance in *H. pylori*, gastroenterologists should treat *H. pylori* as an infectious disease and change the empiric *H. pylori* treatment paradigm to an antimicrobial susceptibility testing-guided precision treatment. We recommend that in all *H. pylori* patients, if an endoscopy is performed, one gastric biopsy from the antrum and one from the corpus should be routinely sent to a professional *H. pylori* laboratory for culture and susceptibility testing to tailor the eradication regimen. As with other infectious diseases, antimicrobial stewardship programs for *H. pylori* should be implemented locally, regionally, and nationally to monitor the *H. pylori* antibiotic resistance pattern.[8]

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Conflict of interest statement

None declared.

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