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Helicobacter pylori infection and antibiotic resistance: a WHO high priority?

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Abstract

The WHO listed *Helicobacter pylori* among 16 antibiotic-resistant bacteria that pose the greatest threat to human health. Given the alarmingly high *H. pylori* antibiotic resistance rates, antibiotic stewardship programmes need to be developed and implemented. Future research should explore provider and systems-level barriers to *H. pylori* antibiotic susceptibility testing.

The current situation

On 27 February 2017, the WHO published a list of 16 antibiotic-resistant bacteria that pose the greatest threat to human health. They listed three priorities: critical, high and medium. *Helicobacter pylori* was categorized as a high-priority bacteria in the same tier as vancomycin-intermediate or resistant, and methicillin-resistant *Staphylococcus aureus. H. pylori* infects 50% of the world's population and accounts for >95% of gastric cancers[1]. Gastric cancer is the third most common cause of cancer death worldwide. Importantly, *H. pylori* infection has become increasingly difficult to cure owing to the increase in antimicrobial resistance. The WHO publication was designed to guide and promote research and development of new antibiotics. However, it behoves us to examine how we, as clinicians, might also be contributing to antibiotic resistance and how we can better manage antibiotic use.

Owing to the increase in antibiotic-resistant *H. pylori* infection, empiric triple therapies — a PPI and two antibiotics (amoxicillin plus clarithromycin, metronidazole or a fluoroquinolone) — no longer reliably achieve high cure rates. Current recommendations now restrict their empiric use to areas with a low local prevalence of antibiotic resistance and for patients who have not taken an antibiotic in the same class[1]. These antibiotics can still be used when the infecting strain is known to be susceptible[1].

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Competing interests statement

D.Y.G. is a consultant for RedHill Biopharma regarding novel *H. pylori* therapies and has received research support for culture of *H. pylori* and is the principal investigator of an international study of the use of antimycobacterial therapy for Crohn's disease. He is also a consultant for BioGaia in relation to probiotic therapy for *H. pylori* infection and for Takeda in relation to *H. pylori* therapies. B.N.D. declares no competing interests.

Lack of *H. pylori* treatment success has rarely led to a change in therapy or guideline recommendations. For example, despite longitudinal studies showing consistently low cure rates over 15 years at the University of Michigan, USA (79.6% during 2001–2005 versus 78.2% during 2011–2015), clinicians continued to prescribe clarithromycin triple therapy[2]. By 2000, the cure rate with clarithromycin-containing triple therapy had fallen to 80% or less, yet guidelines continued to recommend clarithromycin triple therapy as first-line empiric therapy until 2016 (REF. 1). In Japan, clarithromycin resistance now approaches 50% and yet clarithromycin-containing triple therapy as recently as early 2017 was reaffirmed as the first-choice anti-*H. pylori* therapy[3,4].

Importantly, new *H. pylori* treatment guidelines discuss resistance, but also inadvertently promote misuse of antibiotics[1,2,5]. In Western countries, clarithromycin and metronidazole resistance are individually common, whereas dual resistance remains rare[4]. This aspect led recent USA, Canadian and European *H. pylori* treatment guidelines to recommend concomitant therapy, a four-drug regimen consisting of a PPI plus amoxicillin, metronidazole and clarithromycin. This regimen is functionally identical to giving metronidazole and clarithromycin triple therapies simultaneously[1–5]. The basis for the recommendation was clinical effectiveness, but the strategy is actually based on the hope that the infection will be susceptible to either clarithromycin or metronidazole. Concomitant therapy might better be named ‘Hope Therapy’. In reality, concomitant therapy gives all patients at least one unnecessary antibiotic, therefore, potentially contributing to antibiotic overuse[3] (TABLE 1).

Despite the presence of microbiology laboratories in every hospital and many clinics, *H. pylori* antibiotic susceptibility testing is rarely offered, making local susceptibility patterns unavailable. This lack of knowledge forces clinicians to either make a best guess or prescribe an extra antibiotic[4]. Traditionally, treatment guidelines for *H. pylori* infection have emanated from gastroenterologists who most often recommended fairly ineffective empiric therapies. This approach contrasts with how infectious disease specialists approach bacterial infections, which is to tailor therapy according to bacterial cultures and antibiotic susceptibility testing, ensuring appropriate antibiotic use and optimizing the chance of cure. This lack of reliable antibiotic susceptibility data will not be solved until professional societies, health-care payers and providers, and patient advocates ensure widely available *H. pylori* antibiotic susceptibility testing[3,4]. A robust network of local, national and global surveillance systems, similar to those for *S. aureus* and other Gram-negative bacteria, should be established. Such a network is required to track antibiotic prescribing and resistance patterns, and inform strategies for dealing with emerging resistance.

Choosing antibiotics wisely to cure

Although resistance to macrolides, nitroimidazole and fluoroquinolones in *H. pylori* has rapidly increased, amoxicillin, tetracycline and rifabutin remain effective. Although clinical trials with rifabutin are ongoing, a reliable high cure rate regimen has not yet been established. Doxycycline has generally proven ineffective and tetracycline is frequently impossible to obtain due to limited production for human use. Tetracycline is, however, available in a prepackaged form, consisting of bismuth, tetracycline and metronidazole, but

it requires a separate prescription for the PPI. In the USA, this formulation is expensive and packaged for a 10-day course; however, 14-day therapy is recommended in the presence of metronidazole resistance which, along with amoxicillin allergy, is the primary reason for using the combination. Studies also suggest bismuth quadruple therapy might be equally effective with twice daily dosing of bismuth and tetracycline. It might be possible to replace tetracycline with amoxicillin (1 g three times a day), which would increase availability and reduce adverse effects and costs, according to results from a study in China[6]. These modifications have not been evaluated in the West and are not yet optimized in terms of dosing or duration.

Future anti-*H. pylori* antimicrobial therapies will probably include the new PPI, vonoprazan (a competitive acid blocker), which potentially can increase the intragastric pH to near neutral[3,4]. Antibiotics are largely ineffective against metabolically inactive bacteria[4]. *H. pylori* does not multiply at a pH <6 and, instead, can enter a dormant state and survive despite the presence of antibiotics to which it is susceptible. Vonoprazan can theoretically maintain the intragastric pH at ≥6, which cannot be reliably achieved in Western countries using traditional PPIs[4]. At pH 6 or 7, *H. pylori* multiplies and can theoretically be eradicated with a single antibiotic such as amoxicillin[3,4]. The details and reliability of vonoprazan dual therapy remain to be established (for example dose, frequency and optimum duration), but seems to be achievable.

In summary, although we clearly need new antibiotics and non-antibiotic antimicrobial *H. pylori* therapies, it is even more critical that we change practice behaviour regarding the appropriate use of current antibiotics to preserve them for future use. Effective treatment of bacterial infections requires knowing antibiotic susceptibility patterns and tailoring treatment accordingly. Given limited *H. pylori* antibiotic susceptibility data and because most physicians do not know the resistance patterns in their communities, we recommend empiric concomitant four-drug therapy despite the fact that one of the antibiotics is unnecessary. In light of the alarmingly high rate of drug-resistant *H. pylori*, antibiotic stewardship programmes for *H. pylori* should be developed and implemented. Antibiotic susceptibility testing is an essential part of antibiotic stewardship, and future research should explore provider-level and systems-level barriers to performing *H. pylori* antibiotic susceptibility testing. Improving prescribing practices and restricting antibiotic misuse might have far greater impact on human health than any improvement in specific *H. pylori* treatment.

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Table 1

Hypothetical scenario of number of unnecessary drugs for *H. pylori* therapy depending on antibiotic sensitivity patterns

Sensitivity pattern of *H. pylori* to clarithromycin and metronidazole		**Prevalence of pattern**	**Successful treatment of *H. pylori***	**Number of ineffective drugs used**	**Number of unnecessary drugs used**
Clarithromycin: susceptible 80%; resistant 20%	**Metronidazole: susceptible 60%; resistant 40%**				
Susceptible	Susceptible	48%	Yes	0	1
Susceptible	Resistant	32%	Yes	1	1
Resistant	Susceptible	12%	Yes	1	1
Resistant	Resistant	8%	No	2	2

Table showing the number of ineffective or unnecessary antibiotics used by a population of patients similar to that seen in the USA — with the *H. pylori* resistance pattern of 20% resistant to clarithromycin, 40% resistant to metronidazole (8% dual resistance) — that receives concomitant therapy of a four-drug therapy with a PPI, amoxicillin, clarithromycin and metronidazole. All patients will receive at least one unnecessary antibiotic (either clarithromycin, metronidazole, or both) irrespective of the proportions with antibiotic resistance.

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