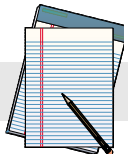

Antimicrobial Susceptibility Testing for *Helicobacter pylori*: Implications for Clinical Practice

Haim Shmuely MD and Yaron Niv MD

Department of Gastroenterology, Rabin Medical Center (Beilinson Campus), Petah Tiqva, and Sackler Faculty of Medicine, Tel Aviv University, Israel

Key words: *Helicobacter pylori*, culture, antibiotic resistance, susceptibility, treatment

IMAJ 2001;3:266–268

Helicobacter pylori infection is one of the most common infections worldwide. It is associated with chronic gastritis, duodenal ulcer disease, gastric ulcer, gastric adenocarcinoma and primary gastric lymphoma [1,2]. HP infection is curable with antimicrobial therapy. Unfortunately, resistance to metronidazole and an increasing resistance rate to clarithromycin have been reported and adversely impact treatment efficacy [3,4]. Recently, HP resistance to amoxicillin and tetracycline was also described [5,6]. However, there is no evidence-based therapeutic choice since no large randomized trials have been performed comparing the highly effective regimens. Currently, optimal therapy consists of a one week combination of a proton pump inhibitor or ranitidine bismuth citrate and two antibiotics: amoxicillin/clarithromycin or amoxicillin/metronidazole (85–95% cure) [7,8]. The large MACH studies have confirmed that the addition of a PPI to the two antibiotics has significantly improved the cure rate of *H. pylori* infection and reduced the impact of antimicrobial resistance [9,10]. To guide clinical practice, however, the resistance rate should be determined in each geographic area as well as among different ethnic groups. Triple regimens with metronidazole have proven less effective for infections with primary metronidazole-resistant strains [9,10].

In the previous issue of *IMAJ* (March 2001, page 163), Avidan and colleagues enhance our understanding of HP eradication in patients who failed one week triple therapy. In phase I of their study [11], the investigators compared two treatment regimens: bismuth-subcitrate, amoxicillin and metronidazole (BAM) with lansoprazole, clarithromycin and metronidazole (LCM), each administered for 7 days. Although triple therapy with bismuth salt and two antibiotics has been widely used, it has been surpassed by triple therapy with PPI. PPIs are directly inhibitory to *H. pylori* [12], act as potent urease inhibitors [13], and are very effective at inhibiting acid secretion, which permits better antimicrobial efficacy. It may not be advisable, however, to use triple therapy with LCM as a first-line treatment in an area with a high prevalence of metronidazole resistance [Y. Niv, Maastricht II Guidelines, personal communication] such as Israel [14]. Although the combination of clarithromycin and metronidazole is very effective, patients who are not cured have at least single, and usually double, resistance [15,16], and there is no logical treatment afterwards. If a first-line clarithromycin-based regimen fails, a metronidazole-based regimen may be used as a second-line treatment, and vice versa.

Avidan et al. [11] achieved a successful HP eradication rate, namely 89% and 95% in patients treated with BAM and LCM, respectively. The sample size was small and included 42 and 43 patients in each treatment arm. In phase II of the study, 10 were failures of phase I, 8/42 and 2/43, respectively, and were unsuccessfully treated with one week triple therapy. The results of phase I clearly indicate that LCM is superior to BAM as a first-line treatment. However, the authors do not stipulate whether their patients had been treated previously or had other variables associated with metronidazole resistance [17]. In phase II of the study, the overall ineffectiveness of both metronidazole-based regimens is in concordance with the previously reported *in vitro* sensitivity data showing a high frequency of a resistance of HP to metronidazole [14]. Earlier studies of larger series revealed a 21–33% rate of HP resistance to metronidazole in patients prior to treatment, and a 47% rate in patients after treatment failure [18,19]. The latter is much lower than the 100% (4/4 culturable biopsies) found by Avidan et al. None of the drug regimens currently in use to treat HP eradicate the infection in 100% of patients, not even quadruple therapy with a PPI twice a day combined with a bismuth compound, tetracycline and metronidazole [20,21].

HP is inherently resistant to only a few antimicrobial drugs (i.e., vancomycin, nalidixic acid, trimethoprim and sulfona-

HP = *Helicobacter pylori*
PPI = proton pump inhibitor

mides), but becomes readily resistant to metronidazole, and to a lesser extent, clarithromycin, if either agent is given alone [22,23]. It rarely becomes resistant to luminally active agents such as bismuth, tetracycline and amoxicillin. Luminal acidity influences the effectiveness of some drugs against HP. Raising the gastric pH level from 3.5 to 5.5 increases the *in vitro* effectiveness of amoxicillin and clarithromycin more than tenfold [24]. This may explain the effectiveness of regimens that contain a PPI.

When HP infection is diagnosed by endoscopy, clinicians usually rely on histology or rapid urease testing rather than on cultures, which are less sensitive and require experienced laboratory personnel. Moreover, even when the first treatment attempt fails, a second-line regimen is used before the results of the gastric biopsy culture are available. Clinicians can calculate the need for biopsy according to the known triple-therapy and quadruple-therapy success rate in their region. After administration of a second-line therapy, based on culture findings, failure is expected in one out of 100 patients.

In the current climate of expanding indications for treatment, combined with the increased cost-consciousness in healthcare, evidence has already been amassed in favor of empirical therapy based on the results of non-invasive tests [25]. This strategy dictates the performance of even fewer HP cultures, which are reserved only for resistant HP strains after two to three eradication trials. However, if ongoing studies confirm the high treatment failure rate in cases of infection with clarithromycin-resistant HP or even amoxicillin-resistant strains, then culture and susceptibility testing may become more important.

Regardless of the clinical value of susceptibility testing of HP, further research into the mechanisms and prevalence of antibiotic resistance will likely lead the way toward the development of new antimicrobial agents as well as new modalities of treatment, such as therapeutic vaccination.

It is difficult to recommend a specific antibiotic combination in an area where metronidazole or clarithromycin resistance is unknown. Clinical trials are needed, as with a new penicillin for *Streptococcus pneumoniae* in a population with variable percentages of penicillin-resistant organisms. We need to know the effectiveness of different combinations for sensitive and resistant organisms separately as well as the association between the *in vitro* sensitivity and the *in vivo* effect. This information should be required of all treatment trials.

The rise in antibiotic resistance emphasizes the need for community surveillance of HP sensitivity as in other important infectious diseases. These data will allow physicians to choose the therapy appropriate for their patients.

References

1. Parsonnet J. *Helicobacter pylori. Infect Dis Clin North A*m 1998;12:185–97.
2. Crump M, Gospodarowicz M, Shepherd FA. Lymphoma of the gastrointestinal tract [Review]. *Semin Oncol* 1999;26:324–37.
3. van der Wouden EJ, Thijs JC, van Zwet AA, Sluiter WJ, Kleibeuker JH. The influence of *in vitro* nitroimidazole resistance on the efficacy of nitroimidazole-containing anti-*Helicobacter pylori* regimens: a meta-analysis. *Am J Gastroenterol* 1999;94:1751–9.
4. Dore MP, Leandro G, Realdi G, Sepulveda AR, Graham DY. Effect of pretreatment antibiotic resistance to metronidazole and clarithromycin on outcome of *Helicobacter pylori* therapy: a meta-analytical approach. *Dig Dis Sci* 2000;45:68–76.
5. Kwon DH, Kim JJ, Lee M, Yamaoka Y, Kato M, Osato MS, El-Zaatari FAK, Graham DY. Isolation and characterization of tetracycline-resistant clinical isolates of *Helicobacter pylori*. *Antimicrob Agents Chemother* 2000;44:3203–5.
6. DeLoney CR, Schiller NL. Characterization of an *in vitro*-selected amoxicillin-resistant strain of *Helicobacter pylori*. *Antimicrob Agents Chemother* 2000;44:3368–73.
7. Graham DY. Therapy of *Helicobacter pylori*: current status and issues. *Gastroenterology* 2000;118:S2–8.
8. Kuipers EJ, Kilnkenberg-Krol K. *Helicobacter pylori*, acid and omeprazole revisited: bacterial eradication and rebound hypersecretion. *Gastroenterology* 1999;116:479–83.
9. Megraud F, Lehn N, Lind T, Bayerdorffer E, O'Morain C, Spiller R, Unge P, van Zanten SV, Wrangstadh H, Burman CF. Antimicrobial susceptibility testing of *H. pylori* in a large multicenter trial: The MACH 2 Study. *Antimicrob Agents Chemother* 1999;43:2747–52.
10. Malfertheiner P, Bayerdorffer E, Diete U, Gil J, Lind T, Misiuna P, O'Morain C, Sipponen P, Spiller RC, Stasiewicz J, Treichel H, Ujszaszy L, Unge P, Zanten SJ, Zeijon L. The GI-MACH study: the effect of 1 week omeprazole triple therapy on Helicobacter pylori infection in patients with gastric ulcer. *Alment Pharmacol Ther* 1999;13:703–13.
11. Avidan B, Melzer E, Keller N, Bar-Meir S. The effect of culture results for Helicobacter pylori on the choice of treatment following failure of initial eradication. *IMAJ* 2001;3;163–5.
12. Iwahi T, Satoh H, Nakao M, Iwasaki T, Yamazaki T, Kubo K, Tamura T. Lansoprazole, a novel benzimidazole proton pump inhibitor and its related compounds have selective activity against *Helicobacter pylori*. *Antimicrob Agents Chemother* 1991;35:490–6.
13. Nagata K, Satoh H, Iwahi T, Shimoyama T, Tamura T. Potent inhibitory action of the gastric proton pump inhibitor lansoprazole against urease activity of *Helicobacter pylori*: unique action selective for *H. pylori* cells. *Antimicrob Agents Chemother* 1993;37:769–74.
14. Avidan B, Weiss B, Chowers Y, Younash A, Bar-Meir S, Keler N. Sensitivity and resistance of *Helicobacter pylori* to antibiotic treatment. *Harefuah* 1999;137:272–4 (Hebrew).
15. Buckley MJM, Xia HX, Hyde DM, Keane CT, O'Morain CA. Metronidazole resistance reduces efficacy of triple therapy and leads to secondary clarithromycin resistance. *Dig Dis Sci* 1997;42:2111–15.
16. Katelaris PH, Jones DB. Testing for *Helicobacter pylori* infection after antibiotic treatment. *Am J Gastroenterol* 1997;92:1245–7.
17. European Study Group on Antibiotic Susceptibility of *Helicobacter pylori*. Results of a multicentre European survey in 1991 of metronidazole resistance in *Helicobacter pylori*. *Eur J Clin Microbiol Infect Dis* 1992;11:777–81.
18. Weel JFL, van der Hulst RWM, Gerrits Y, Tytgat GNJ, van der Ende A, Dankert J. Heterogeneity in susceptibility to metronidazole among *Helicobacter pylori* isolates from patients with gastritis or peptic ulcer disease. *J Clin Microbiol* 1996;34:2158–62.
19. Jorgensen M, Daskalopoulos G, Warburton V, Mitchell HM, Hazell SL. Multiple strain colonization and metronidazole resistance in *Helicobacter pylori*-infected patients: identification from sequential and multiple biopsy specimens. *J Infect Dis* 1996;174:631–5.
20. Chiba N, Hunt RH. Bismuth, metronidazole and tetracycline and acid suppression in *H. pylori* eradication: a meta-analysis. *Gut* 1996;39 (Suppl 2):A36–7.
21. van der Hultst RW, van der Ende A, Homan A, Roorda P, Dankert J, Tytgart JN. Influence of metronidazole resistance on efficacy of quadruple therapy for *Helicobacter pylori* eradication. *Gut* 1998;42:166–9.

22. Cederbrant G, Kahlmeter G, Ljungh A. Proposed mechanism for metronidazole resistance in *Helicobacter pylori*. *J Antimicrob Chemother* 1992; 29:115–20.
23. Peterson WL, Graham DY, Marshall B, Blaser MJ, Genta RM, Klein PD, Stratton CW, Denec J, Prokocimer P, Siepman N. Clarithromycin as monotherapy for eradication of *Helicobacter pylori*: a randomized, double-blind trial. *Am J Gastroenterol* 1993;88:1860–4.
24. Dunn BE, Cohen H, Blaser MJ. *Helicobacter pylori*. *Clin Microbiol Rev* 1997;10:720–41.
25. Goddard AF, Logan RPH, Atherton JC, Hawakey CI, Spiller RC. Maastricht Consensus Report regimen for second-line treatment of *H. pylori*: how does it perform in practice? *Gut* 1997;41(Suppl 1):A96.

Correspondence: Dr. Y. Niv, Head, Dept. of Gastroenterology, Rabin Medical Center (Beilinson Campus), Petah Tiqva 49100, Israel. Phone: (972-3) 937-7237, Fax: (972-3) 921-0313, email: yniv@clalit.org.il